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Total Synthesis of Tetrahydrohomofredericamycin A

by

Xianglong Kong

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A thesis submitted to the faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY

Department of Chemistry

Edmonton, Alberta

Spring, 1995

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Faculty of Graduate Studies and Research

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled TOTAL SYNTHESIS OF TETRAHYDROHOMO-FREDERICAMYCIN A submitted by XIANGLONG KONG in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

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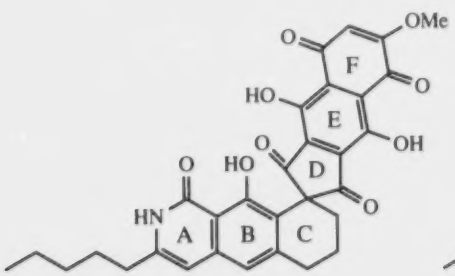
April 12, 1995

Abstract

The total synthesis of tetrahydrohomofredericamycin (**1**), an analog of the natural product fredericamycin A, in which the C-ring has been expanded from a five-membered ring to a six-membered ring, and the side chain has been saturated, was completed. The simpler analogue **2** was also prepared, and both compounds have been submitted for biological evaluation as anticancer agents. The six-membered C-ring confers additional conformational mobility on the spiro system, compared with fredericamycin A itself, and it is of interest to establish if this change is reflected in a change in biological activity, especially as the spirodiketone system of fredericamycin A represents a unique feature among antitumor agents.



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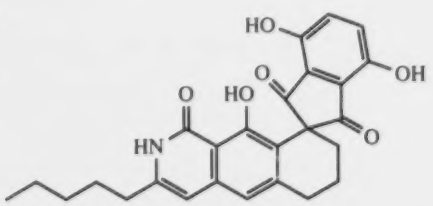
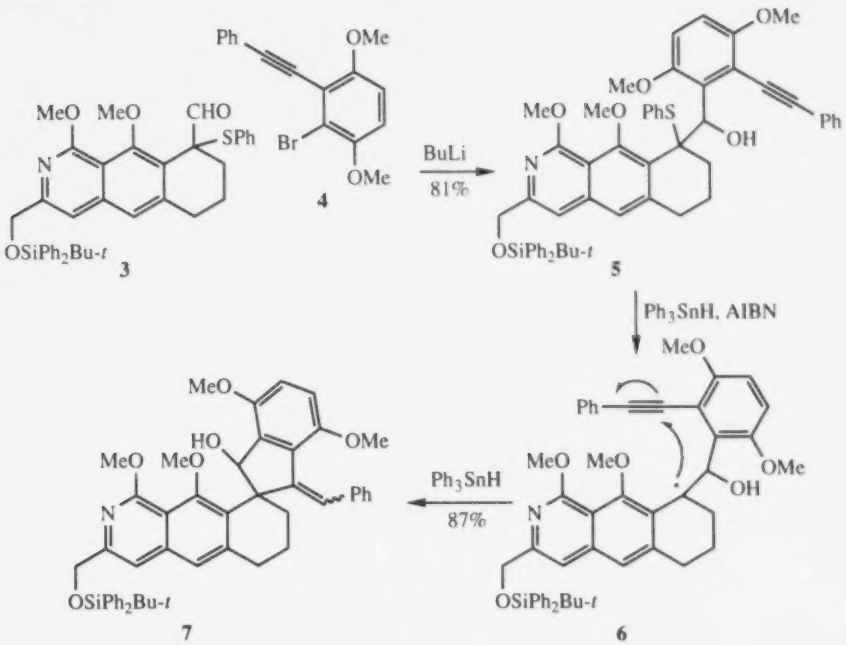


2

A radical methodology for the construction of the sterically congested spiro[4,5]decane structures of **1** and **2** was developed in this synthetic work (Scheme A).

Scheme A


Ph
OMe
MeO
MeO
CHO
SPh
Br
OMe
N
OSiPh2Bu-t
3
4
BuLi
81%
OMe
MeO
MeO
MeO
PhS
OH
Ph
N
OSiPh2Bu-t
5
Ph3SnH, AIBN
MeO
Ph
MeO
MeO
OMe
OH
N
OSiPh2Bu-t
6
Ph3SnH
87%
MeO
HO
OMe
MeO
MeO
Ph
N
OSiPh2Bu-t
7

Acknowledgments

I would like to thank Dr. D. L. J. Clive for his constant encouragement during the course of my graduate studies.

I want to express my gratitude to the staff of the Chemistry Department, especially to those in the NMR, IR, MS and Microanalysis Laboratories.

I also extend my appreciation to Dr. Y. Tao for stimulating discussions and a sample of bromide **337** that was used in preliminary experiments.

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Figure 1 Strategy for the synthesis of spiro carbocycles. 3

List of Abbreviations

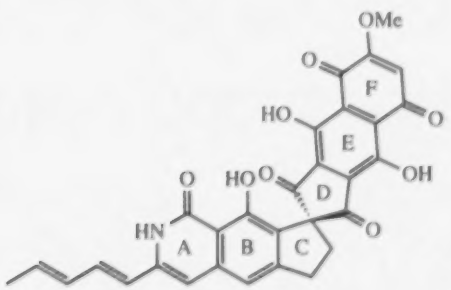
acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
9-BBN-H	9-borabicyclo[3.3.1]nonane
Bn	benzyl
CAN	ceric ammonium nitrate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBALH	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
HMPA	hexamethylphosphoric triamide
m-CPBA	*m*-chloroperoxybenzoic acid
MOM	methoxymethyl
NMO	4-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
TBAF	tetrabutylammonium fluoride
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyran
p-TsOH	*p*-toluenesulfonic acid

I INTRODUCTION

Fredericamycin A – chemistry and biology

Fredericamycin A was isolated from *Streptomyces griseus* by scientists[1] at the Frederick Cancer Research Institute, Maryland, in 1981. It was shown to possess potent *in vitro* cytotoxic activity as well as *in vivo* anticancer activity and is also an antibiotic.[2] Little is known about how fredericamycin A exerts its antitumor or antibiotic action, although recent work has shown that the compound is an inhibitor of DNA processing enzymes topoisomerase I and II.[2d]

The structure of fredericamycin A[3] was determined by spectroscopic characterization and confirmed by X-ray crystallographic analysis. However, the absolute configuration for the only center of asymmetry of fredericamycin A remains undetermined.



(±)-1

The biosynthesis of fredericamycin A has been studied,[4] at least to the extent of establishing that all the carbons, except that of the *O*-methyl group, are derived from acetate,

but the more difficult questions of how the spirosystem is formed and whether the molecule is assembled from one or from two chains have not been answered.

The spiro[4,4]nonane system[5] in fredericamycin A has not been observed in any other type of antibiotic. It imposes certain interesting spatial characteristics (an L-shape) on the molecule, which may have an important role in determining its biological activity, either with respect to its fit into the site of action or by virtue of electronic effects[5] between the two flat components.

General methodologies for the construction of spiro carbocycles

The central structure of fredericamycin A is a spiro[4,4]nonane system. In addition, spiro[4,5]decane and spiro[5,5]undecane systems constitute the basic carbon framework found in the sesquiterpenes, spirovetivane, acorane and chamigrane classes. In general, spiro carbocycles represent challenging targets in natural product synthesis.[6]

The strategies used for the construction of spirosystems[6b] can be classified into five conceptually different approaches (Figure 1).

1. Synthesis of a quaternary carbon center, followed by intramolecular cyclization.

2. Direct construction of the spirosystem via intramolecular spirocyclization.

3. Two-directional spirocyclization or intramolecular

cycloaddition to build up in one step the spirocenter and one of the two rings associated with the spirocenter.

4. Synthesis of a tricyclic system followed by specific bond breakage to release the desired spirosystem.

5. Formation of spirocycles by rearrangement.

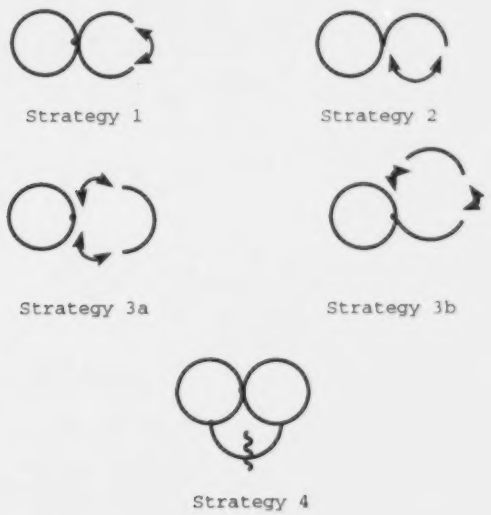


Figure 1 Strategy for the synthesis of spiro carbocycles

For an asymmetric synthesis, the major stereochemical problem is establishing the correct sense of chirality at the spirocenter related to other asymmetric centers presented in one or both rings.

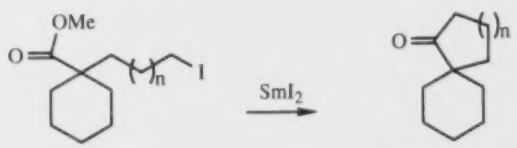
Synthesis of the quaternary carbon center followed by intramolecular cyclization

There are two extensive reviews on the synthesis[6] and asymmetric synthesis[7] of quaternary carbon centers, and in

the following section I will deal mainly with the different intramolecular cyclizations used to construct spirocycles from appropriate quaternary centers.

Intramolecular nucleophilic cyclization

Molander developed a samarium(II) iodide-promoted reductive cyclization of haloalkyl acyl derivatives,[8] for the construction of [4,5]decane and [5,5]undecane spirosystems (eq. 1). This reaction is very mild and selective, as



2 3 eq. 1

n = 1 93%

n = 2 91%

alkyl chloride units, acetals, and olefins remain completely intact under the reaction conditions.

A very similar approach[9] was used by Schakel to make a spiroketone (eq. 2). Here, the anion was generated via halogen-metal exchange.

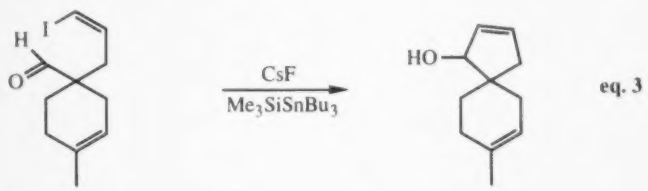
4 5 eq. 2

n = 1 67%

n = 2 66%

Mori reported an intramolecular cyclization involving

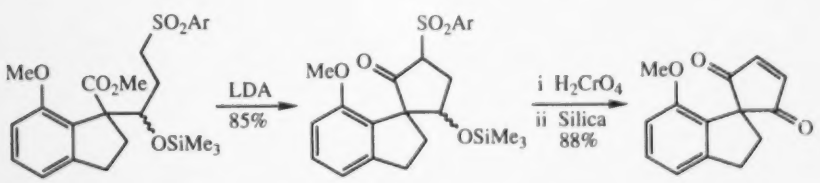
addition of a vinyl anion to carbonyl groups[10] including aldehyde, ketone, and ester, and he applied the method in the synthesis of spiro sesquiterpenes, a simple model study being shown in eq. 3. The vinyl anion was generated from the corresponding vinyl halide by halogen-metal exchange using stannyl anion.



6 7 eq. 3

In one of our own early approaches to the spirodiketone system representing the central structure of fredericamycin A, an intramolecular cyclization of a sulfone-stabilized anion was used[11] for the construction of the spirocenter (Scheme 1).

Scheme 1



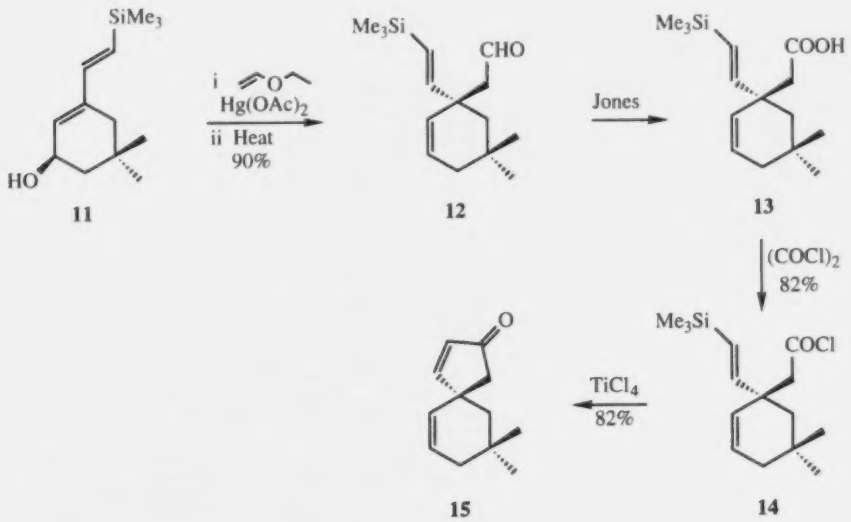
8 **9** **10**

The anion, generated by deprotonation of sulfone **8**, cyclized onto the ester group producing the spiroketone **9**. Jones oxidation, followed by flash chromatography on silica,

then furnished the desired spirodiketone **10**.

Burke used a vinylsilane-mediated spiroannulation, for synthesis of a spiro[4,5]dienone (Scheme 2).[12]

Scheme 2



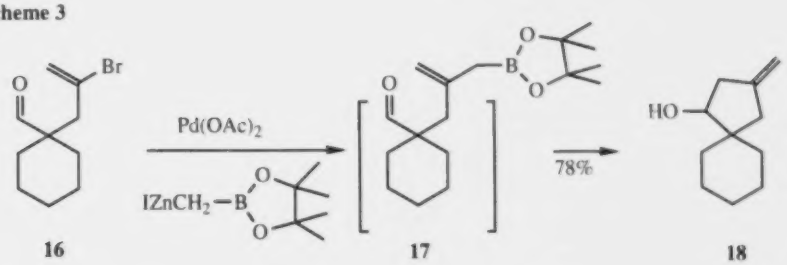
11 **12** **13** **14** **15**

Allylic alcohol **11** was subjected to standard mercuric ion-catalyzed exchange with ethyl vinyl ether, and thermolysis then resulted in efficient Claisen rearrangement to yield **12**. Conversion of **12** to **14** was effected by Jones oxidation to the acid **13** followed by treatment with oxalic chloride to give the corresponding acid chloride **14**. Finally, Lewis acid catalyzed spiroannulation provided the desired dienone **15**.

Very recently, Miyaura and Suzuki disclosed a new intramolecular allylboration-cyclization of oxoallyl borates, generated *in situ* by a palladium-catalyzed cross-coupling

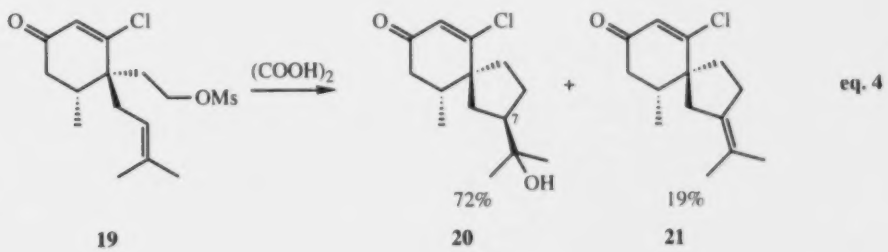
reaction of halo carbonyl compounds (Scheme 3).[13]

Scheme 3



π-Cation cyclization

In synthetic studies on spirovetivanes, Murai used a π-cation intramolecular cyclization[14] to generate a spiro[4,5]decane structure (eq. 4).

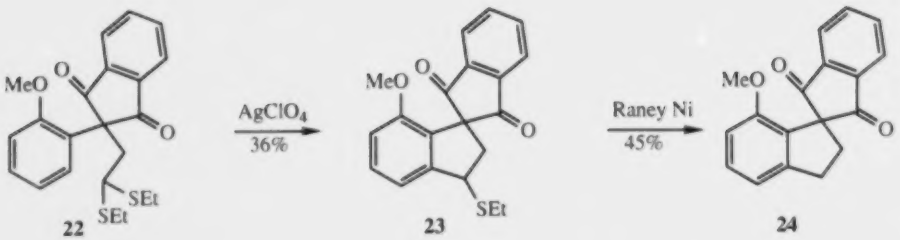


eq. 4

Treatment of mesylate **19** with oxalic acid afforded spiroketone **20** with the desired relative configuration along with some dehydrated product **21**.

An intramolecular Friedel-Crafts reaction of a thioacetal[15] was described by Braun for the synthesis of a spiroketone related to the four central rings of fredericamycin A (Scheme 4).

Scheme 4

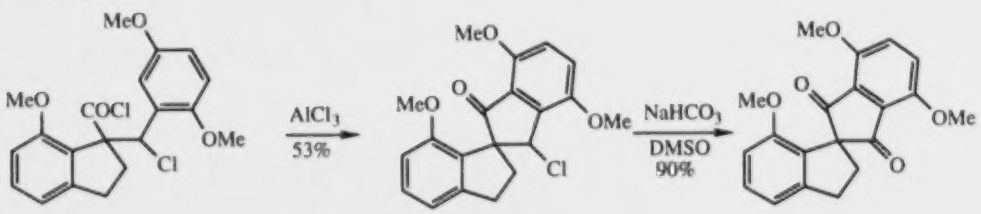


22 23 24

Lewis acid catalyzed Friedal-Crafts reaction of **22** gave spirocyclic material **23**, which was subsequently desulfurized with Raney nickel to the tetracyclic diketone **24**.

Julia relied on a similar intramolecular Friedel-Crafts acylation[16] for construction (Scheme 5) of spiroketone **27**, which is also related to the central part of fredericamycin A.

Scheme 5



25 26 27

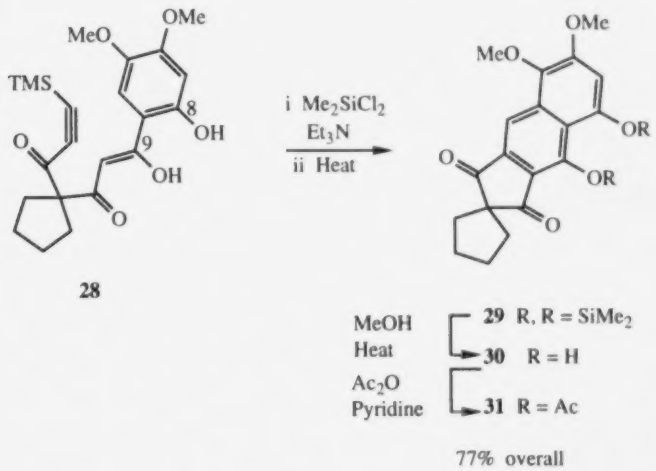
Treatment of acyl chloride **25** with aluminum chloride gave ketone **26**, which was then converted smoothly into spirodiketone **27**.

Intramolecular Diels-Alder reaction

An unusual intramolecular Diels-Alder approach was used

independently by Terashima[17a] and Kita[17b] to construct the spirodiketone structure of an advanced model of fredericamycin A (Scheme 6).

Scheme 6



The oxygens at C-8 and C-9 in **28** were protected as a cyclic silyl ether prior to thermal intramolecular Diels-Alder reaction. After desilylation (**29**→**30**) and protection as a diacetate, the tetracylic product **31** was isolated in 77% overall yield from **28**.

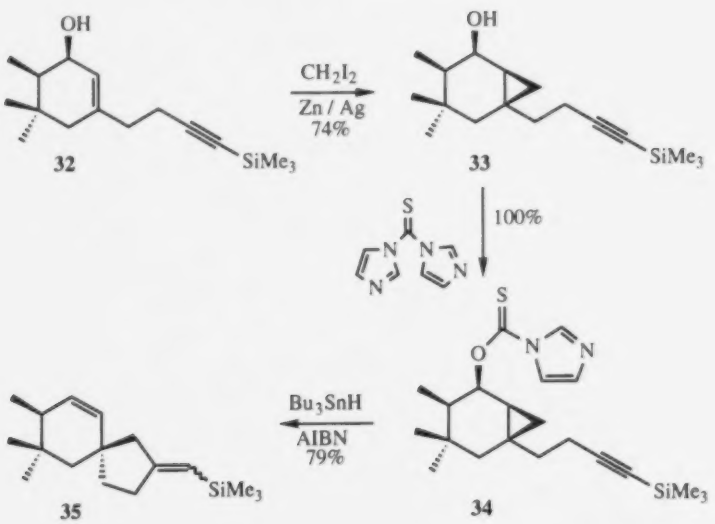
Radical cyclization

Over the past decade, radical chemistry has become a powerful tool for carbon-carbon bond formation in organic synthesis.

An elegant tandem free radical cyclopropylcarbinyl rearrangement-cyclization strategy,[18] was developed for the

regio- and stereospecific construction of spiro-fused carbocycles.

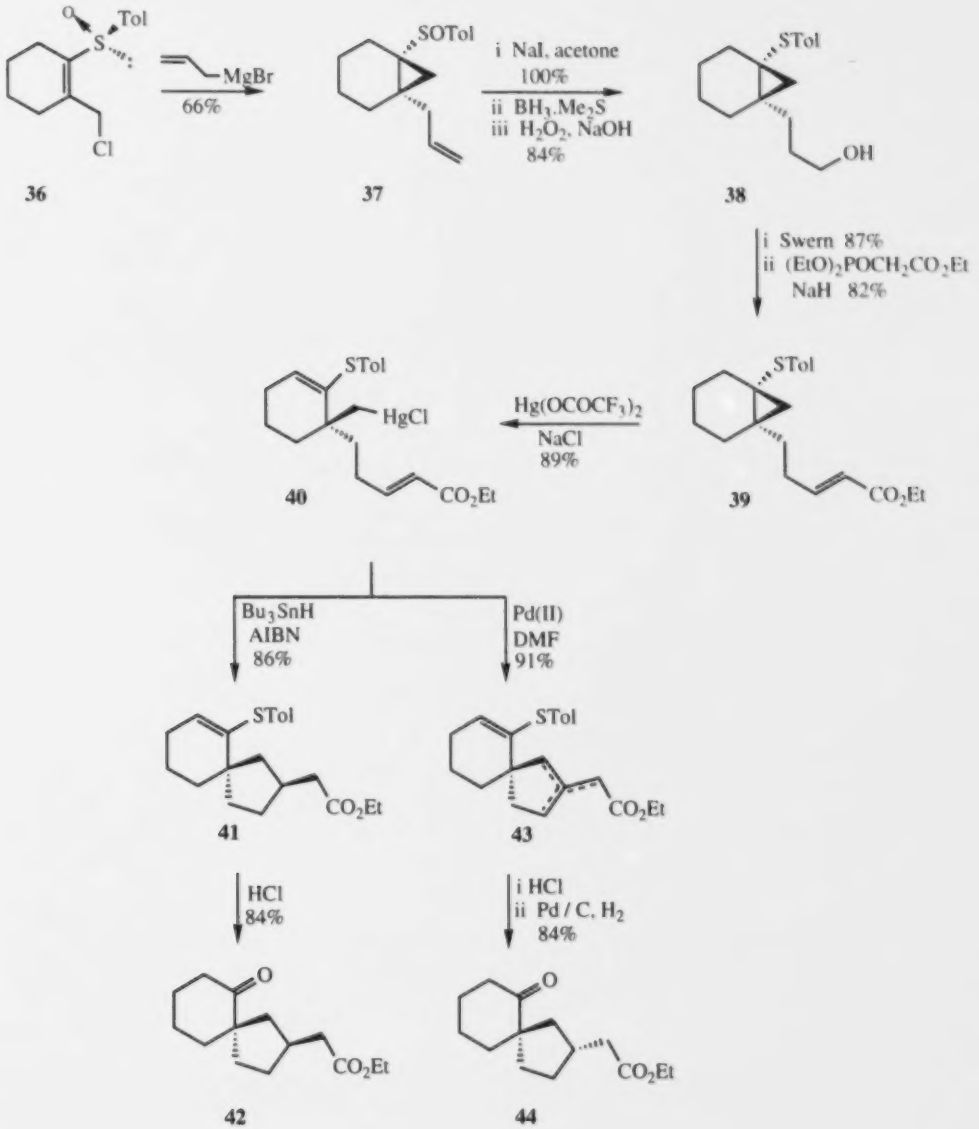
Scheme 7



As shown in Scheme 7, hydroxyl-directed Simmons-Smith cyclopropanation furnished the bicyclic cyclopropylcarbinol **33**. Quantitative conversion to the corresponding thiocarbonyl imidazolide **34** yielded a suitable precursor for radical generation. Finally, transformation via reductive deoxygenation of **34** with tributyltin hydride generated stereospecifically the spirocyclic compound **35** (apparently as a single isomer).

Iwata developed an asymmetric cyclopropanation using an optically pure sulfoxide. Application of this methodology in conjunction with radical cyclization led to an asymmetric construction of a spiro[4,5]decane system (Scheme 8).[19]

Scheme 8



Asymmetric cyclopropanation of chiral sulfoxide **36** furnished olefin **37**, which was converted into **39** by reduction of the sulfoxide and chain extension by standard methods. Ring opening of cyclopropane **39** with mercury trifluoroacetate gave rise to the desired α,β-unsaturated alkylmercury

chloride **40** in a highly regioselective manner. Cyclization of **40** under standard conditions proceeded smoothly to provide the spiro[4,5]decane derivative **41**. This was subsequently hydrolyzed to give ketone **42** as the major product. Interestingly, palladium-catalyzed cyclization of **40** afforded a mixture of spiro compounds, which were converted to **44** by hydrolysis and hydrogenation.

Direct intramolecular spirocyclization

This strategy involves an intramolecular cyclization that occurs at what is to become the spirocenter. The spirocenter and one of two rings are formed at same time.

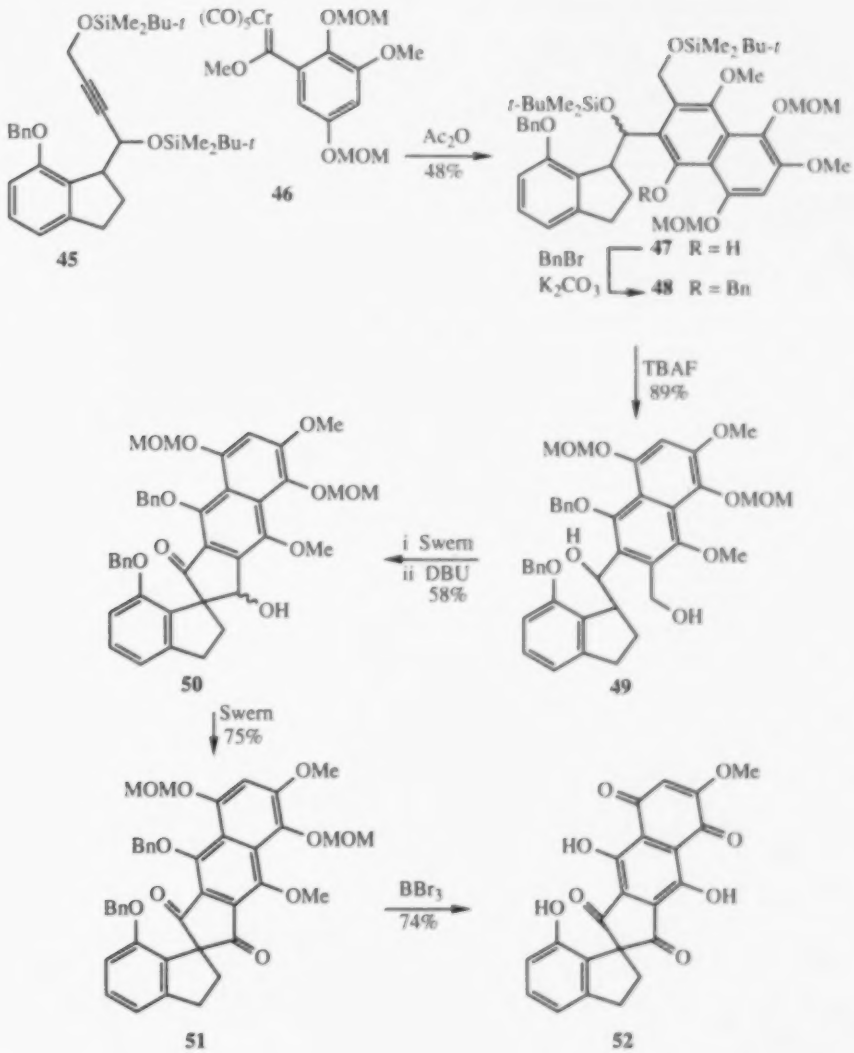
Nucleophilic addition/substitution

The most classical way of direct spirocyclization is by intramolecular aldol condensation.

Boger reported a synthesis of the BCDEF ring system of fredericamycin A, in which the spirodiketone structure was constructed using this approach (Scheme 9).[20]

The EF ring system (as in **1**) was assembled by a benzannulation that relied on an intermolecular reaction between an alkyne and a chromium carbene complex. Subsequent protection of the free phenol of the benzannulation product **47** as a benzyl ether (**47**→**48**) and desilylation of the primary and secondary benzylic alcohols provided diol **49**. Swern oxidation, followed by *in situ* DBU-catalyzed aldol cyclization gave **50**. Swern oxidation (**50**→**51**) and

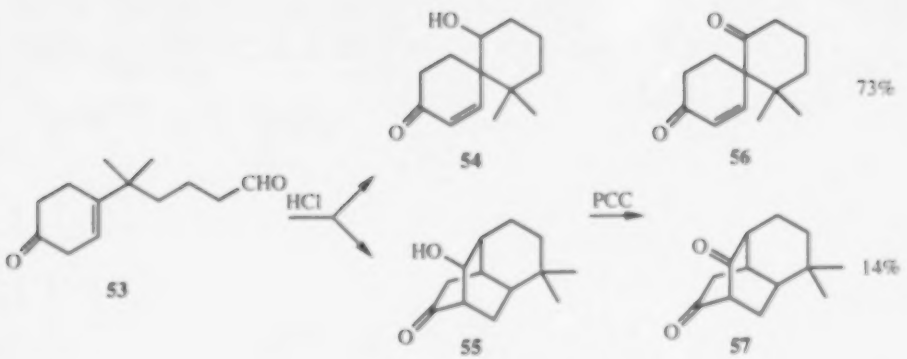
Scheme 9



deprotection (**51→52**) completed the synthesis of the BCDEF ring system of fredericamycin A with all the required functionality.

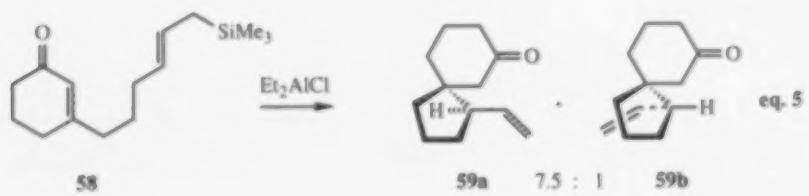
Niwa used an acid catalyzed spiroannulation to construct the spiro[5,5]undecane skeleton (Scheme 10).[21]

Scheme 10



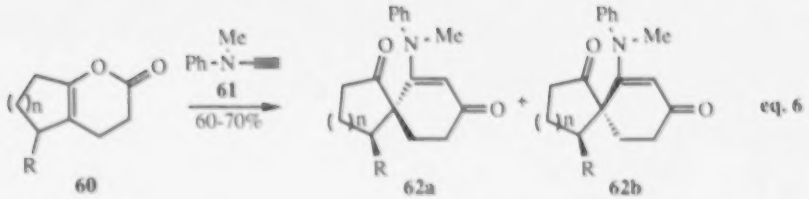
Acid catalyzed cyclization of **53**, gave a 5:1 inseparable mixture of desired spiroenone **54** and tricyclic ketone **55**. Upon oxidation, the spiroketone **56** was separated in 73% yield (from **53**).

A diastereoselective synthesis of a spiro[4,5]decane by the use of an intramolecular Sakurai reaction has also been reported.[22]



Lewis acid catalyzed cyclization of allyl silane **58** gave the desired spiroketone **59a** with high diastereoselectivity (eq. 5).

Ficini and co-workers developed a stereoselective spiroannulation[23] leading to spiro[4,5]decanes and [5,5]undecanes (eq. 6).

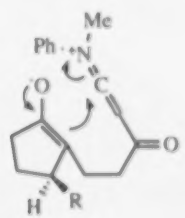


60 62a 62b

n = 2	R = Me	85	15
n = 1	R = Me	80	20
n = 1	R = *i*-Pr	100	

Treatment of enol lactone **60** with aminoacetylene **61** in the presence of magnesium bromide gave spirodiketones **62a** and **62b** (eq. 7). The above results show that the reaction takes place with high stereoselectivity and that this selectivity depends on steric hindrance caused by the R group on the enol lactone **60**. The major isomer **62a** is the one in which the R group is *trans* to the enaminoketone moiety. When the hindrance of R is great enough, as in the case of an isopropyl group, isomer **62a** is the only product isolated.

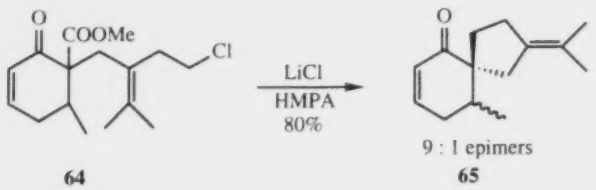
This stereoselectivity can be rationalized by assuming the presence of intermediate **63**, formed after the initial attack of the ynamine on the lactonic carbonyl.



63

In the synthesis of (±)-β-vetivone, Willis described an

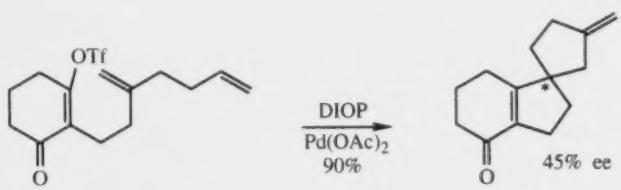
approach to spiroketones **65** (eq. 7) based on intramolecular decarboxylative alkylation.[24] The product was isolated as a 9:1 mixture of epimers.



64 **65** eq. 7

Palladium catalyzed cyclization

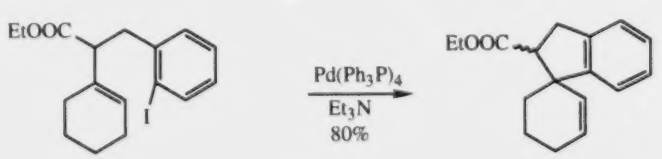
Overman developed a palladium catalyzed double cyclization leading to a chiral spiroenone (eq. 8).[25]



66 **67** eq. 8

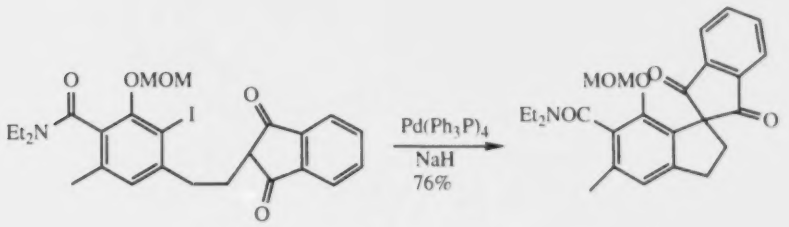
Cyclization of enol triflate **66** with 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane and $Pd(OAc)_2$ afforded **67** with moderate enantioselectivity.

Similarly, Negishi used a palladium catalyzed intramolecular arylation to generate spiro-fused carbocyclic compounds (eq. 9).[26]



68 **69** eq. 9

A new cyclization, involving palladium-catalyzed displacement of halide from aromatic substrates by stabilized enolates,[27] was described by Ciufolini in his synthetic studies towards fredericamycin A (eq. 10).

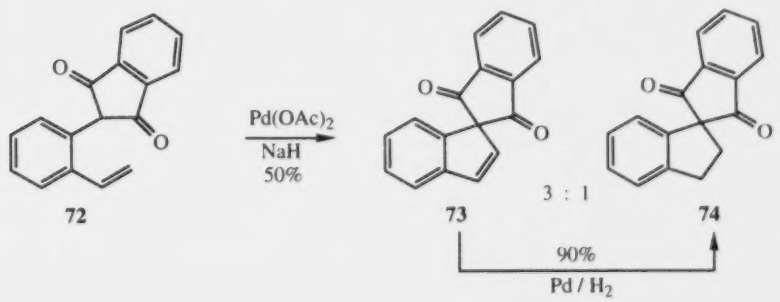


70 **71** **eq. 10**

This reaction permits creation of benzo-fused five- or six-membered rings.

Rama Rao also used a palladium mediated cyclization[28] to construct a spirodiketone (**74**) which represents the central structure of fredericamycin A (Scheme 11).

Scheme 11



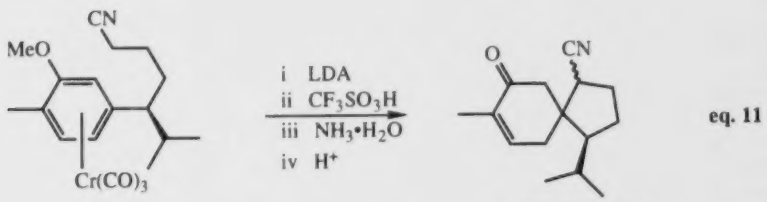
72 **73** **74**

Intramolecular cyclization of the enolate derived from **72**, by the action of sodium hydride, to the double bond provided a mixture of **73** and **74**, and the former could be

hydrogenated to **74** in 90% yield.

Metal complex-mediated cyclization[29,30]

In the synthesis of sesquiterpenes, Semmelhack[30] developed a stereoselective spirocyclization using arene-metal complexes (eq. 11).



40% / 5% mixture

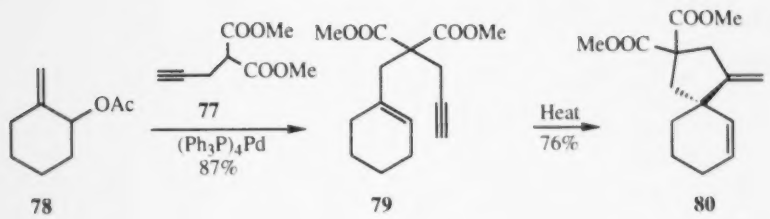
75 **76** eq. 11

The chromium complex **75** was treated with LDA, followed by addition of trifluoromethanesulfonic acid. The resulting red solution was poured into a mixture of aqueous ammonia and ether and, on acidification, the spiro compound **76** was isolated as an 8:1 mixture of diastereoisomers, which was taken further to complete the synthesis of a sesquiterpene.

Ene Reaction

Trost developed a novel annulation via sequential alkylation-Alder ene cyclization (Scheme 12).[31]

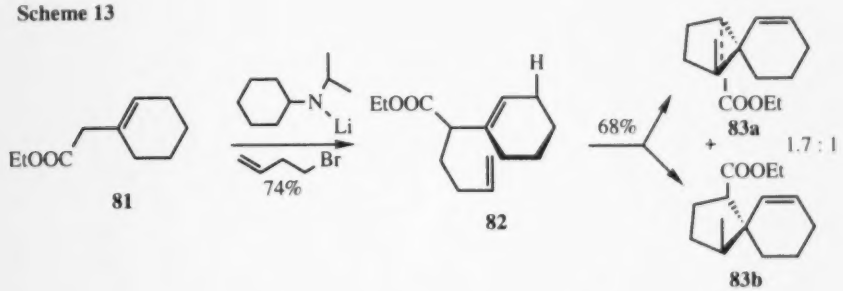
Scheme 12



Alkylation of dimethyl propargyl malonate with the allylic acetate **78** produced **79**, and flash vacuum thermolysis then generated the spiro compound **80**.

In the synthesis of sesquiterpenes, Oppolzer used an intramolecular thermal ene reaction to make the key intermediates[32] (Scheme 13).

Scheme 13



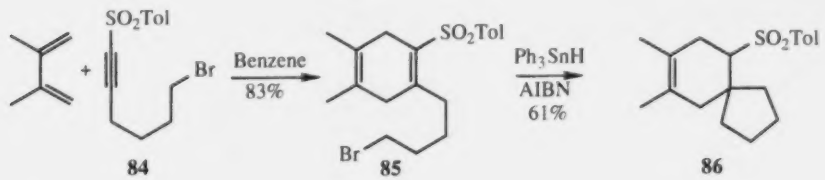
Alkylation of ester **81** gave C-alkylated 1,6 diene **82**. Thermal cyclization of **82** provided a 1.7:1 mixture of **83a** and **83b**. Compounds **83a** and **83b** are separable and interconvertible, and they were further transformed into a number of sesquiterpenes.

Radical Annulation

A sequential intermolecular Diels-Alder reaction and

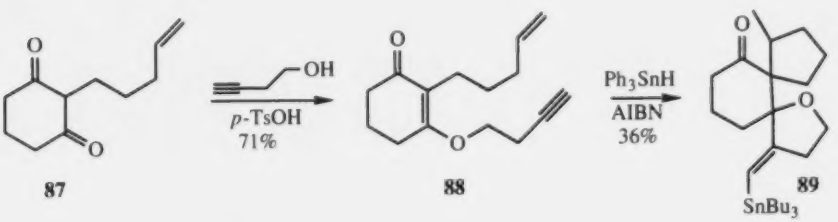
intramolecular radical cyclization[33] has been developed as a convenient approach to linear, bridged, and spiro polycyclic compounds (Scheme 14).

Scheme 14



Simpkins reported a radical chain cyclization[34] in which two spirocenters were generated in one step (Scheme 15).

Scheme 15

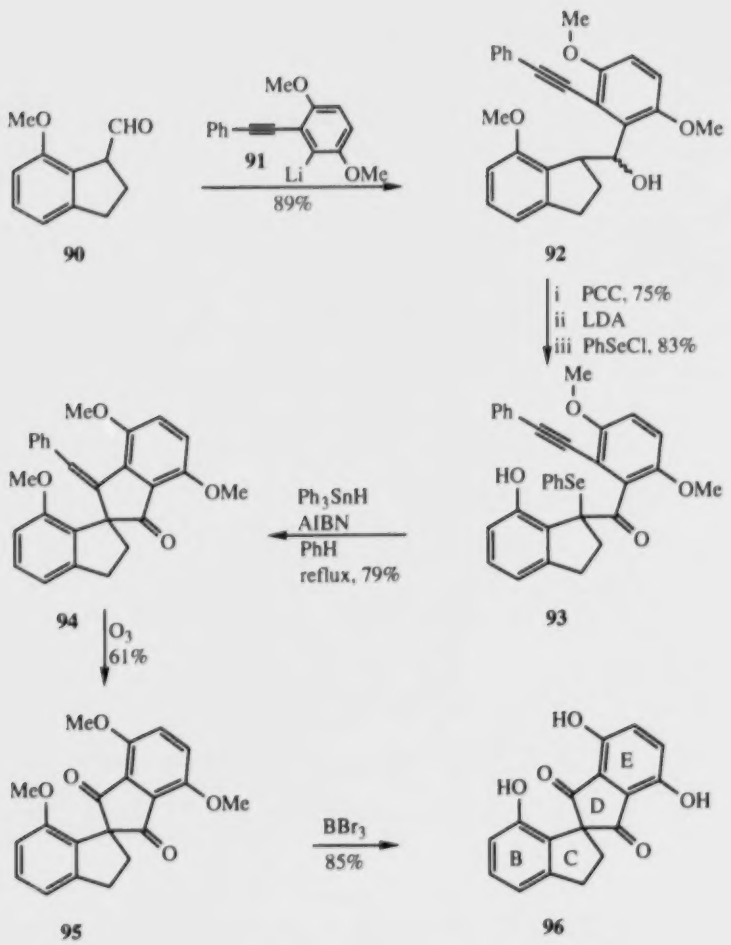


Condensation of diketone **87** with 3-butyn-1-ol provided **88**. Under standard radical cyclization conditions, the tricyclic product **89** was isolated as a single diastereomer. Thus, a new olefin and three new chiral centers were formed in one step with high stereocontrol, although the relative stereochemistry of **89** was not established.

During the synthesis of fredericamycin A in this laboratory, a general method of radical spirocyclization was

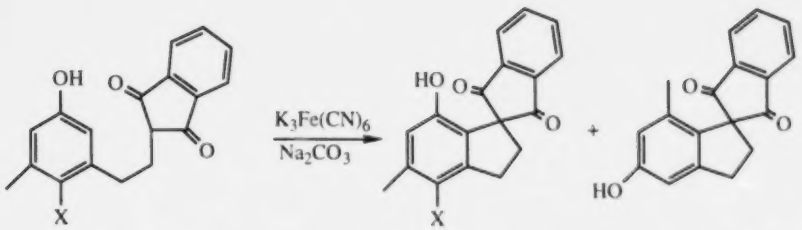
developed to generate the spiro-fused ring system present in the natural product.[35] This synthesis, as shown in Scheme 16, uses an alkyne as a radical acceptor and as a carbonyl synthon. Addition of the aryllithium reagent **91** to the aldehyde **90** gave alcohols **92**. Oxidation and selenation of **92** gave the radical precursor **93**, and radical spirocyclization provided **94** in 79% yield. Oxidative cleavage of the double bond and ether deprotection then afforded **96**, the central part of fredericamycin A.

Scheme 16



Kende and co-workers have developed an oxidative radical coupling reaction of phenolic enolates that was used to make spiro compounds.[36] The synthetic potential of this method is shown in his approach to fredericamycin A, as outlined in Scheme 17.

Scheme 17



97 X = H
100 X = I

NaOAc, *i*-PrOH, 59% → **98** X = H 8%; **101** X = I 46%

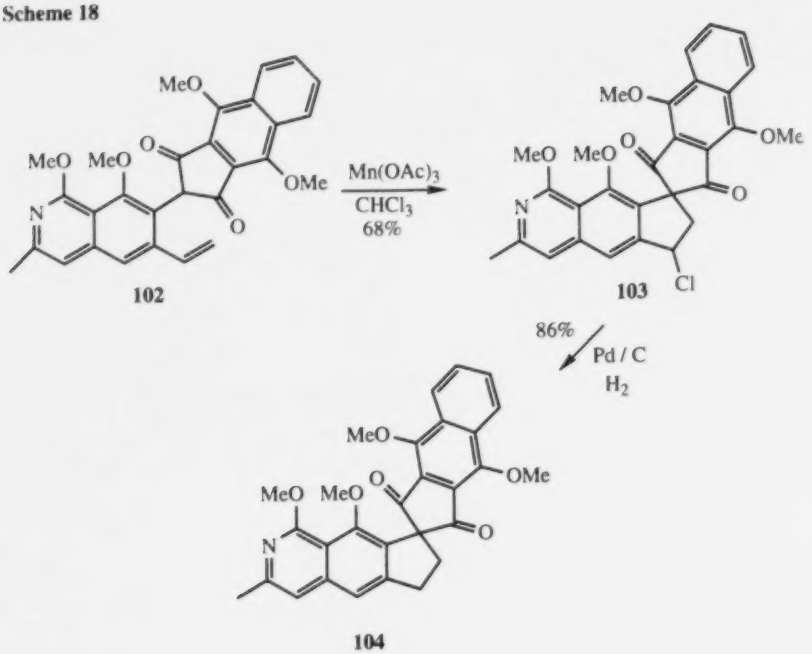
99 67%

Treatment of phenol **97** (X = H) with potassium hexacyanoferrate(II) gave a mixture of **98** and **99**, with the undesired isomer **99** as the major product. The unfavorable regiochemistry could be overcome by blocking the *para*-position with an iodine atom, which could be photochemically removed later. In this case, a 46% yield of the desired *ortho*-coupling product **101** was isolated, and converted (59%) into **98**.

Rama Rao also reported an oxidative radical cyclization as a general approach for constructing the spiro[4,4]nonane structure (Scheme 18).[37]

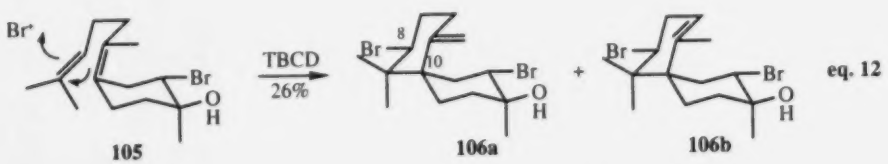
$Mn(OAc)_3$-induced radical cyclization in the presence of chloroform led to chlorodiketone **103**, which was easily dehalogenated by hydrogenolysis.

Scheme 18



π-cation cyclization

Martín described a bromonium ion-initiated intramolecular carbocyclization[38] for the enantioselective construction of the spiro[5,5]undecane system.

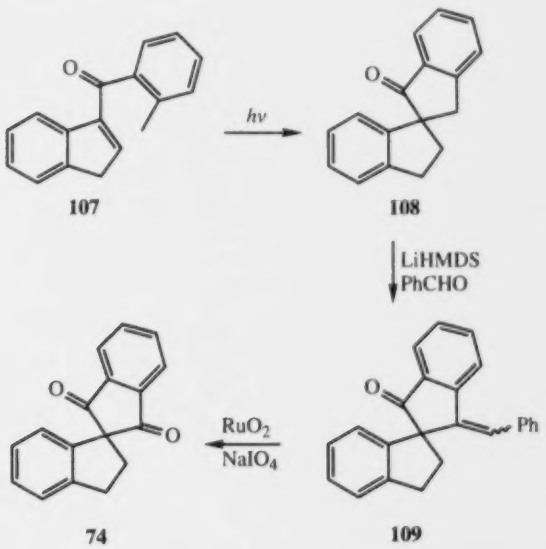


Treatment of optically pure **105** with TBCD (2,4,4,6-tetrabromocyclohexa-2,5-dienone) afforded a 3:1 mixture of **106a** and **106b** (eq. 12). The stereochemistry at C-8 and C-10 was controlled by the preferential low energy chair transition state.

Photochemically-induced cyclization

Mehta[39a] and Pandey[39b] reported a photochemical approach to spirodiketone **74** (Scheme 19).

Scheme 19



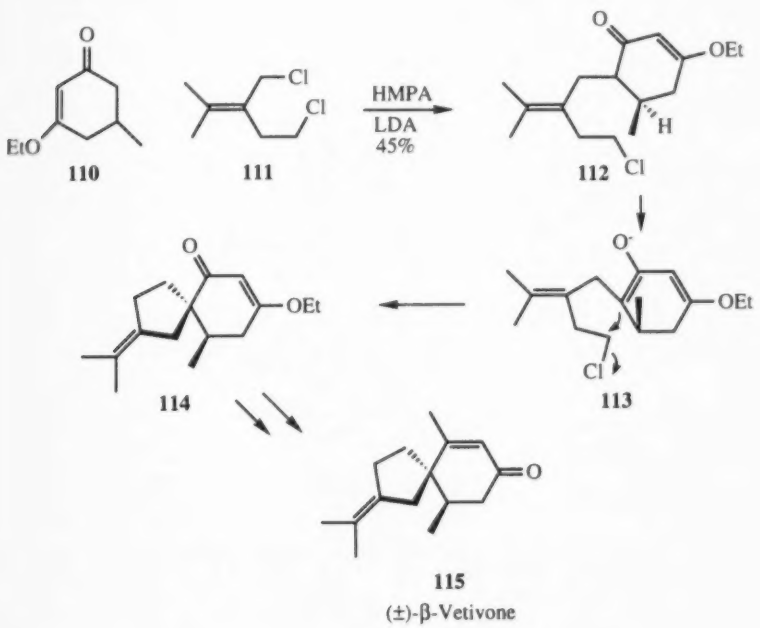
Irradiation of ketone **107** led to formation of spiroketone **108**[39a] via hydrogen abstraction from the methyl group and spirocyclization. The spiro[4,4]nonane derivative **108** was conveniently transformed into the required diketone **74** through the benzylidene derivative **109** and cleavage (**109→74**).

Two directional one-step spiroannulation

Two carbon-carbon bonds and one of the two rings associated with the spirocenter can be formed in a one-step annulation process.

One of the early examples of one-step intermolecular spiroannulation is illustrated in Stork's elegant synthesis of β-vetivone[40] shown in Scheme 20.

Scheme 20

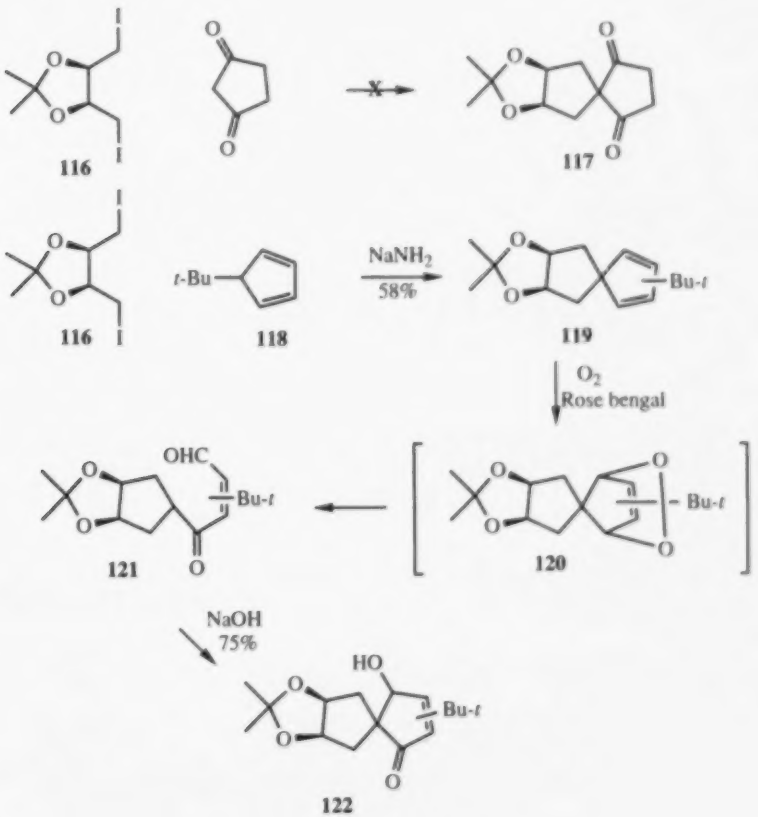


The kinetic enolate of ethyl enol ether **110** was doubly alkylated with dichloride **111** to give a spiroannulated enol ether **114**. The stereochemistry of this annulated enol ether **114** was rationalized as follows: the first alkylation would obviously involve the allylic chloride to give **112**. The subsequent enolate geometry then forces the ring methyl into a pseudo axial conformation and one would expect completion of the ring *trans* to that methyl. This assumption was confirmed by conversion of **114** to β-vetivone.

Another group of natural products that contain a

spiro[4,4]nonane structure is the ginkgolides, which were first isolated from the leaves of the Ginkgo tree and are strong competitive inhibitors of platelet-activating factors (PAF). As in the case of fredericamycin, ginkgolides have a spiro[4,4]nonane system. In the synthesis of this spiro structure, Magnus[41] tried to use double alkylation to construct the spiroketone **117**, but all attempted spiroalkylations failed (Scheme 21).

Scheme 21

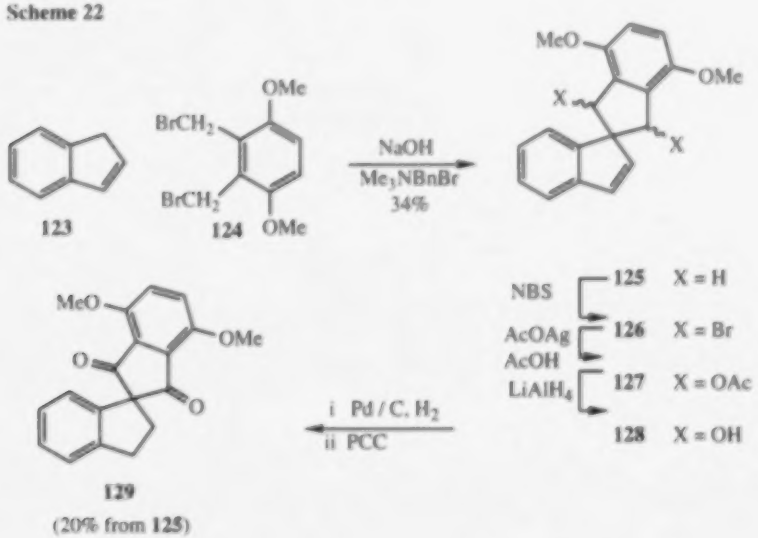


Therefore, an alternative anion, generated from **118** was

examined. Alkylation of cyclopentadiene **118** with the diiodide gave the desired spirocyclic compounds **119** as a mixture of isomers. The oxygen functionality on the diene portion of **122** was introduced by singlet oxygen oxidation (**119→121**) and aldol condensation (**121→122**).

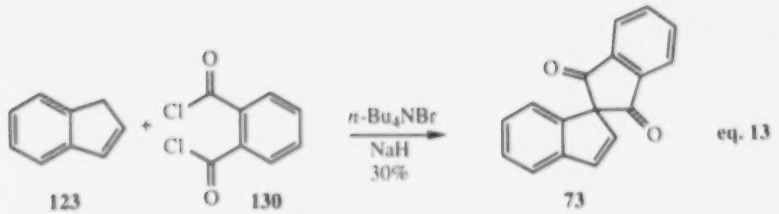
This double alkylation was also used by Julia for the construction of the spiro[4,4]nonane diketone[42] present in fredericamycin A.

Scheme 22



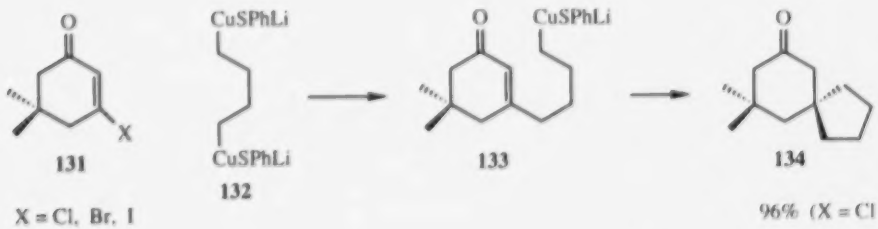
Alkylation of indene under phase transfer catalysis conditions provided spiro compounds **125** which were converted into spirodiketone **129** by the standard operations summarized in Scheme 22.

A more efficient use of this strategy was Ayyanger's diacylation of the indenyl anion (eq. 13).[43]

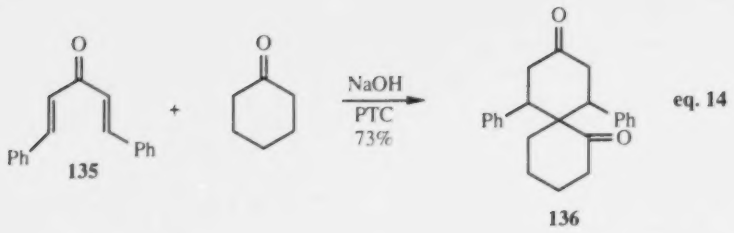


Wender developed an one-step spiroannulation [44] method based on the double Michael addition of β-halocycloalkenones with a novel class of reagents, the organobis(cuprates), as shown in Scheme 23. This method allows for the efficient synthesis of the most commonly encountered spirocyclic systems i.e., spiro[4,4]nonanes, spiro[4,5]decanes, and spiro[5,5]undecanes. This spiroannulation can be accomplished with various substituted β-haloenones and functionalized organobis(cuprates).

Scheme 23



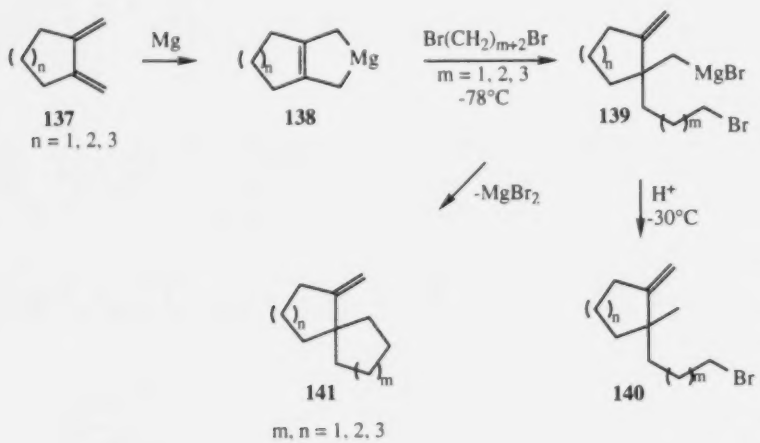
A double Michael addition under phase-transfer conditions was also reported[45] in a one step preparation of spiro compounds (eq. 14).



eq. 14

Rieke developed a one-step spiroannulation, using 1,3-diene-magnesium reagents.[46] His process is comparable to Wender's approach to spirocyclic compounds, involving the reaction of bis(nucleophilic) reagents with bis(electrophilic) acceptors. Reaction of 1,2-bis(methylene)cycloalkenemagnesiums with bis(electrophiles) provided a general and efficient method for the synthesis of commonly-encountered spirosystems.

Scheme 24



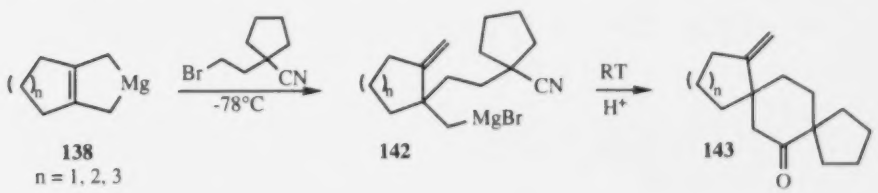
In the first example, the freshly prepared magnesium complex **138** was treated with a 1,n-dibromoalkane, and this procedure resulted in the overall 1,2-cyclization of the

original diene, giving a spirocarbocycle (**141**) in good yield (Scheme 24).

The reaction proceeded through intermediate **139**, which can be trapped by protonation at low temperatures, yielding the corresponding bromo olefin **140**. On the other hand, cyclization occurs upon warming, affording a spirocarbocycle (**141**) containing an exocyclic double bond.

The second example involves the reaction of magnesium reagents with bromoalkyl nitriles and provides keto-functionalized spirocycles **143** (Scheme 25). Trapping the intermediate **142** by protonation at a low temperature afforded the monoalkylated product of the original diene, establishing the position of initial attack.

Scheme 25



138
n = 1, 2, 3

142

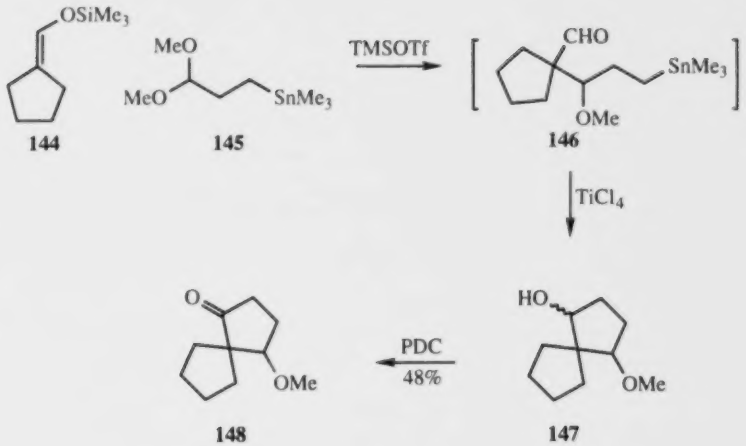
143

Several bifunctional acceptor-donor annulation reagents have been developed for simple preparation of spirocycles.

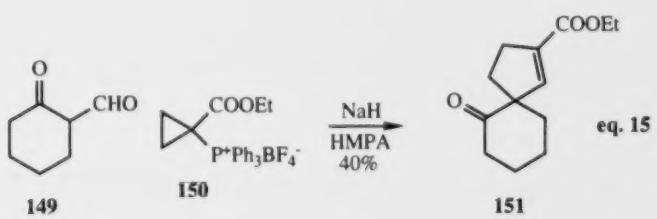
An acetal stannane (**145**) (Scheme 26) was prepared for the construction of spirocycles.[47] Reaction of silyl enol ether **144** with **145** in the presence of TMSOTf gave aldehyde **146**. This cyclized on treatment with $TiCl_4$ to alcohols **147**, which were immediately oxidized to ketone **148** in 48% overall

yield.

Scheme 26



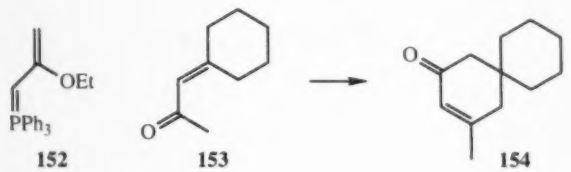
Dauben and Hart developed a route to a variety of 2-substituted spiro[4,5]decanes, based on the reaction of α-formylcycloalkanones, such as (**149**) and Wittig-like reagent **150** (eq. 15).[48]



This reaction presumably involved nucleophilic attack of the enolate on the geminally activated cyclopropane to produce a stabilized phosphorus ylide which then underwent a regiospecific intramolecular Wittig reaction at the aldehyde carbonyl group. This spiroannulation process was used in the

synthesis of a number of naturally occurring sesquiterpenes.

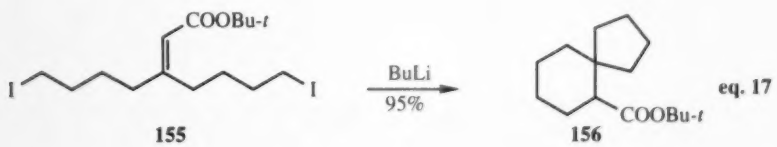
Martin reported the annulation agent **152** (eq. 19).[49] Reaction of **152** with α,β-unsaturated ketone **153** allows construction of monocyclic, fused bicyclic, and spirocyclic ring systems. For example, Michael addition of **152** to **153**,



152 **153** **154** eq. 16

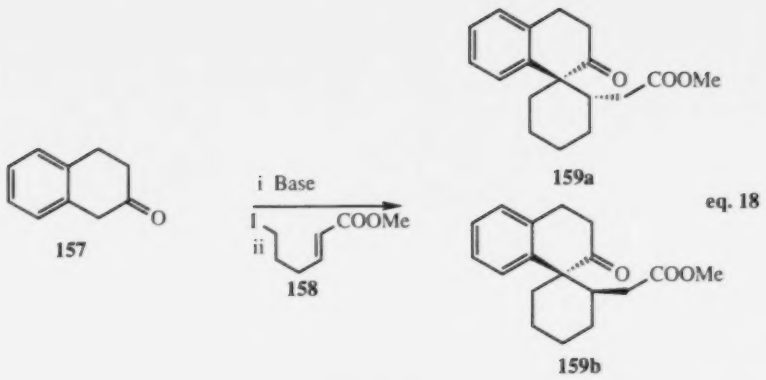
followed by *in situ* intramolecular Wittig reaction, gave spirocyclohexenone **154** (eq. 16).

A sequential intramolecular Michael addition-alkylation approach was reported by Cooke as a route to spirocycles (eq. 17).[50] This process involves halogen-metal exchange, intramolecular Michael addition and, finally, cycloalkylation.



155 **156** eq. 17

In synthetic studies related to the homoerythrina alkaloids, d'Angelo disclosed a stereoselective spiroannulation based on a tandem alkylation-Michael addition sequence (eq. 18).[51] This efficient process allows formation of the spirocenter and two rings in a single step.



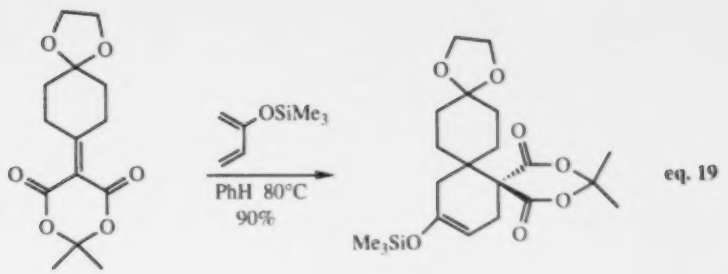
eq. 18

As illustrated in eq. 18, condensation of iodoester **158** with the sodium enolate of **157**, generated with NaH, gave the spiroester as a 1:1 mixture of diastereomers in 68% yield. However, when sodium hydride was replaced by cerium carbonate, the only product was **159a**, isolated in 66% yield.

The stereochemical outcome was attributed to the result of kinetic control, possibly directed by chelation of the ester group of the hexenoate appendage by the cesium counterion of the tetralone enolate.

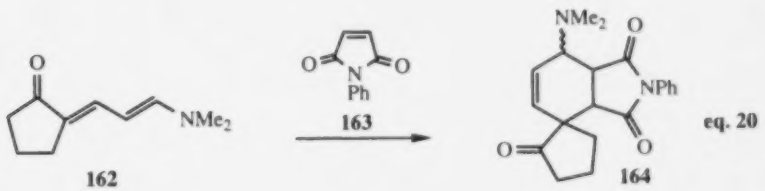
Cycloadditions

Holmes reported a Diels-Alder approach to a spirocyclic intermediate that should lead to aphidicolin[52] (eq. 19). The oxygen functionality on the diene not only activated the diene but also provided the required carbonyl function in the Diels-Alder product.



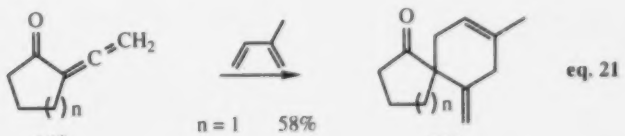
160 161 eq. 19

A cyclic dienaminone **162** (eq. 20) was synthesized as an intermediate in a route to spirocarbocyclic compounds.[53] Treatment of **162** with the dienophile **163** gave spiro compounds **164**.



162 164 eq. 20

The Lewis acid-catalyzed Diels-Alder reaction of α-ethenylidenecyclanones[54] has been developed as a highly stereoselective route to spirodieneones (eq. 21).



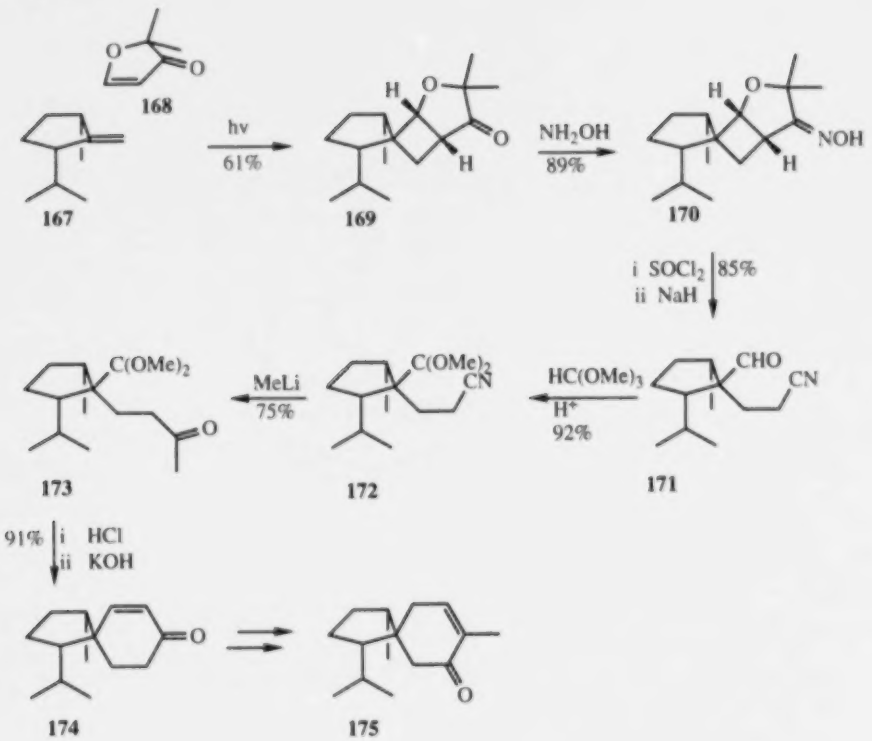
165 166 eq. 21

n = 1 58%
n = 2 69%
n = 3 63%

In the synthesis of the optically active sesquiterpene (-)-acorenone, Baldwin used a 2+2 photochemical cycloaddition

as the key step to form a spirocyclic structure **169** (Scheme 27).[55]

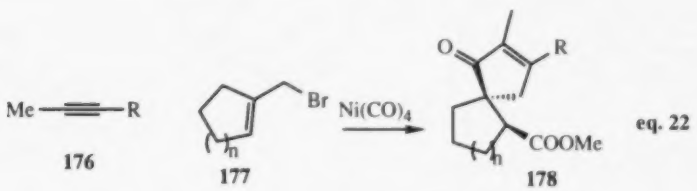
Scheme 27



Optically active olefin **167** was irradiated in the presence of furanone **168** to afford adduct **169** as a single isomer. The cycloaddition occurred exclusively from the less hindered face of **167**, away from the isopropyl group in a head-to-tail manner. The adduct **169** was converted in six steps to the desired spiro[4,5]decane **174**. The sequence involved Beckmann rearrangement of oxime **170** to a hydroxynitrile which, in turn, underwent retroaldol ring

opening on exposure to base to give aldehyde **171**, which is the precursor to nitrile acetal **172**. After conversion of the nitrile to methyl ketone **173**, and hydrolysis of the acetal, the resulting ketoaldehyde was smoothly cyclized by the action of base to enone **174**, which was further converted to (-)-acorenone **175**.

Moretó developed a $Ni(CO)_4$-promoted intermolecular carbonylative cycloaddition.[56] This reaction provided a general method for the synthesis of fused and spiro-fused cyclopentenones (eq. 22).



eq. 22

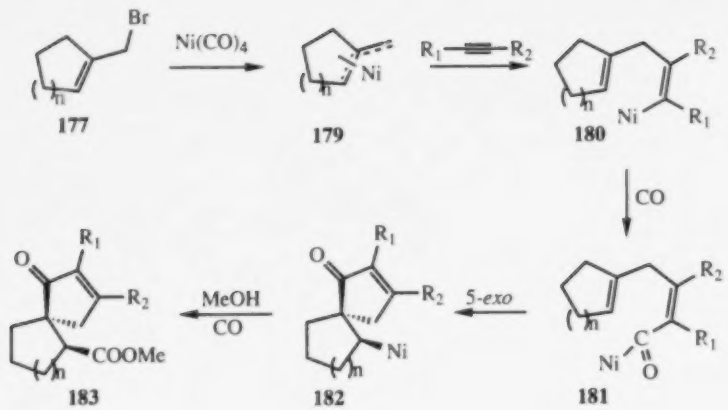
	R = CH_2OH	R = COOMe
n = 1	50%	45%
n = 3	75%	42%

In this reaction, more than four bonds are built under very mild conditions and with high regio- and stereocontrol.

The mechanism is shown in Scheme 28. The first step is formation of a cyclic π-allyl nickel complex **179** which, after insertion into the alkyne, gives a vinylnickel intermediate **180**. This intermediate undergoes fast CO insertion to afford an acylnickel complex **181**. Stereoselective 5-*exo* trigonal ring closure then results in a cycloalkylnickel complex, which leads to the product **183**, after CO insertion and

methanolysis.

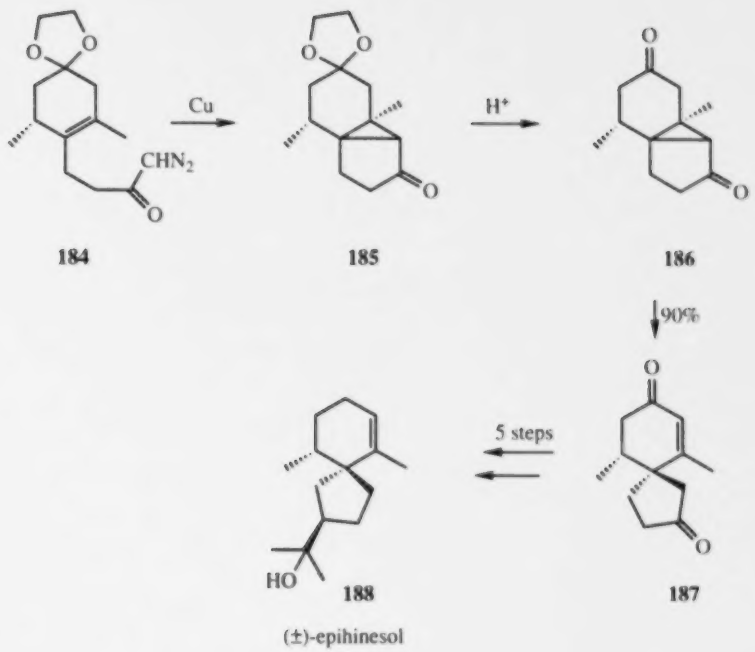
Scheme 28



Construction of spiro carbocycles by fragmentation of tricyclic compounds.

Intramolecular cyclopropanation followed by cleavage of an exterior cyclopropane bond leads to a spiro framework. This synthetic strategy has been used as a key step in the construction of a number of naturally occurring spiro sesquiterpenes. The first elegant application of this protocol, which led to the total synthesis of (±)-hinesol and (±)-epihinesol (**188**), was achieved by Deslongshamps[57] (Scheme 29).

Scheme 29



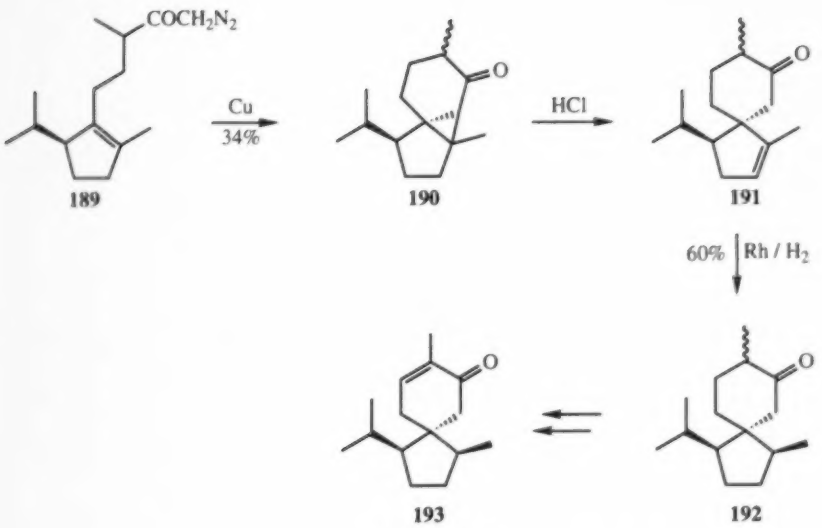
184 **185** **186** **187** **188**

(±)-epihinesol

Catalytic decomposition of keto diazoketone **184** gave a mixture of *cis* and *trans* isomers in a 9:1 ratio. Both isomers can be obtained in pure form by chromatography. The pure *cis* isomer **185** was treated with acid to give the bicyclic enediketone **187**, which was further converted to (±)-epihinesol **188**.

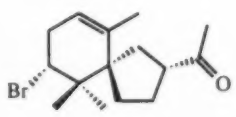
This spiroannulation process had also been investigated by White,[58] and applied, for example, to the stereocontrolled synthesis of (-)-acorenone B (Scheme 30).

Scheme 30



Copper-catalyzed intramolecular cyclopropanation of **189** occurred at the less hindered side of the double bond, yielding a tricyclic structure **190**. Exposure of **190** to HCl in chloroform then gave olefin **191**. From that point, hydrogenation occurred exclusively from the side opposite to the isopropyl substituent to provide **192** in 60% yield. Compound **192** was then converted to (-)-acorenone B in several steps.

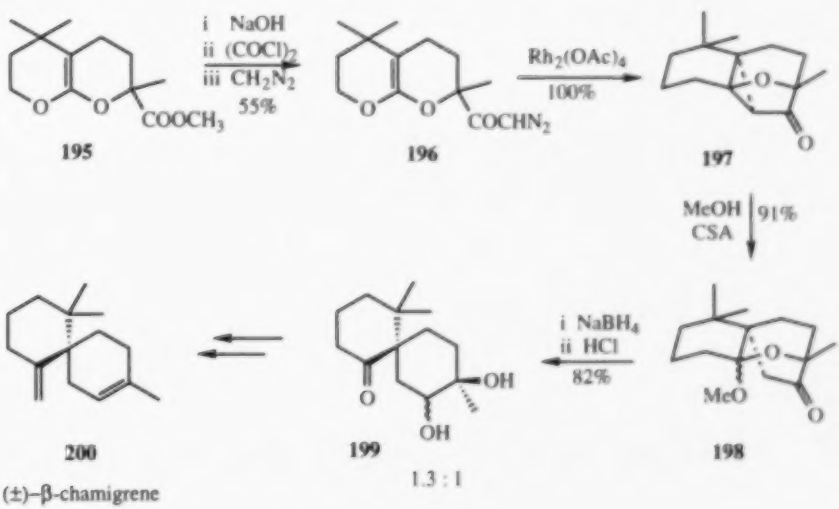
(±)-Spirolaurenone (**194**) has also been synthesized by the same strategy.[59]



194
(±)-spirolaurenone

Adams reported a stereoselective synthesis of β-chamigrene[60] (Scheme 31). The transannular cyclopropanation of a ketocarbenoid, generated by $Rh_2(OAc)_4$ catalysis, on a bicyclic dihydropyran nucleus **196** (which was easily made from ester **195**), provided the key oxatricyclic ketone intermediate **197** needed for the synthesis of the [5,5] spirocyclic system. Selective fragmentation of the cyclopropane followed by hydrolytic cleavage of the C-O bond provided the spirocycle **199** as a mixture of epimers. Both isomers were then converted into β-chamigrene **200**.

Scheme 31

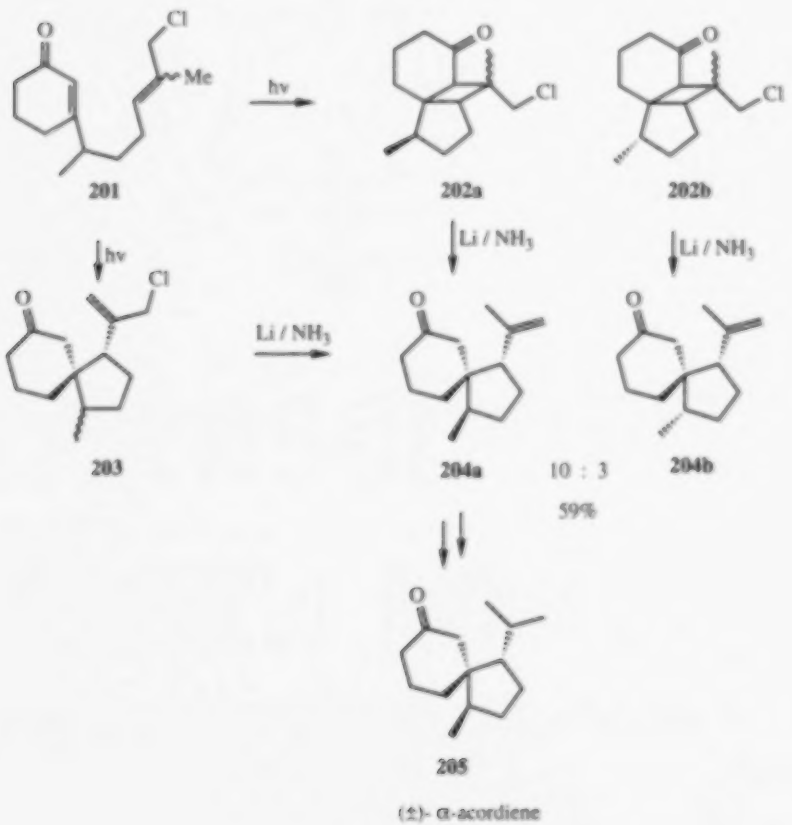


195 **196** **197** **198** **199** 1.3 : 1 **200** (±)–β-chamigrene

Intramolecular photoaddition, in conjunction with reductive fragmentation, has provided a regio- and stereoselective approach to spirocyclic compounds. Oppolzer[61a] used this strategy in the synthesis of (±)-α-acordiene (Scheme 32). Irradiation of **201** afforded a mixture

of three compounds, **202a**, **202b**, and **203** in a ratio of 1:5:3, which, on reductive cleavage, furnished spiroketones **204a** and **204b** in 59% yield as a 10:3 separable mixture. The major isomer (**204a**) was further transformed into (±)-α-acordiene **205**.

Scheme 32

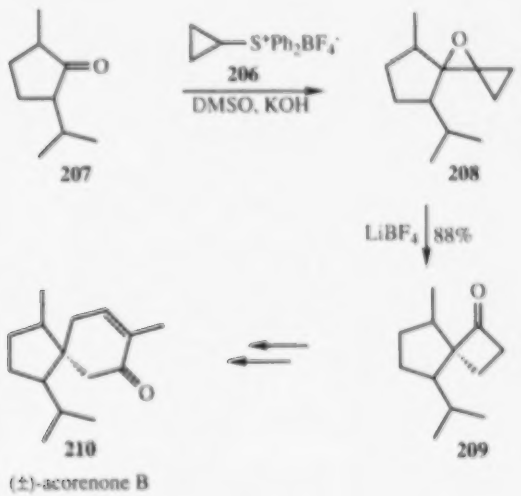


Rearrangement

Trost developed a general strategy of cyclobutanone spiroannulation[62] and the method has been used in the total synthesis of a variety of natural products.

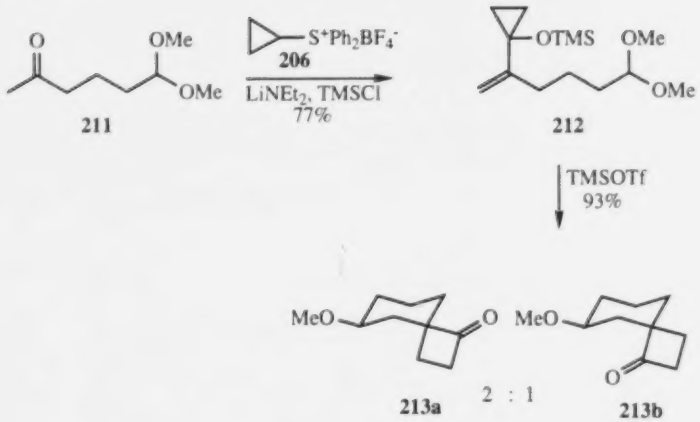
Spiroannulation with **206**, followed by rearrangement of the resulting oxaspiropentane, gave spirocyclobutanone **209**[63a] (Scheme 33), which was further elaborated to (±)-acorenone B (**210**) in several steps.

Scheme 33



A similar version of this approach is illustrated in Scheme 34.[63b] The ketoacetal **211** was converted to the requisite silyl ether **212**, and exposure to a catalytic amount of TMSOTf provided the cyclized product as a mixture of **213a** and **213b** in a 2:1 ratio.

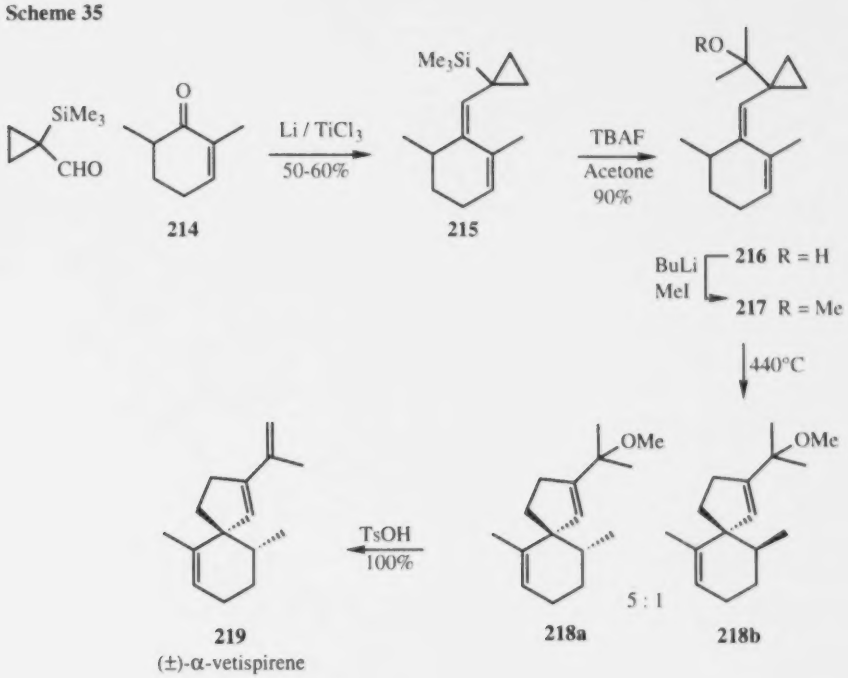
Scheme 34



Thermal rearrangement of a vinyl cyclopropane has been reported by several groups as a general approach to spiro carbocycles.[64-66] α-Vetispirene, a [4,5]spirobicyclic sesquiterpene, was made by an efficient five-step synthesis, in which the spirocenter was constructed by rearrangement of a vinyl cyclopropane (**215**).[64]

As shown in Scheme 35, McMurry coupling gave vinyl cyclopropane **215**, which was refluxed with TBAF and acetone to effect desilylation and alkylation (**215→216**). Following conversion to methyl ether **217**, thermal rearrangement produced a mixture of **218a** and **218b** in a 5:1 ratio. Compound **218a** was converted into (±)-α-vetispirene upon exposure to TsOH.

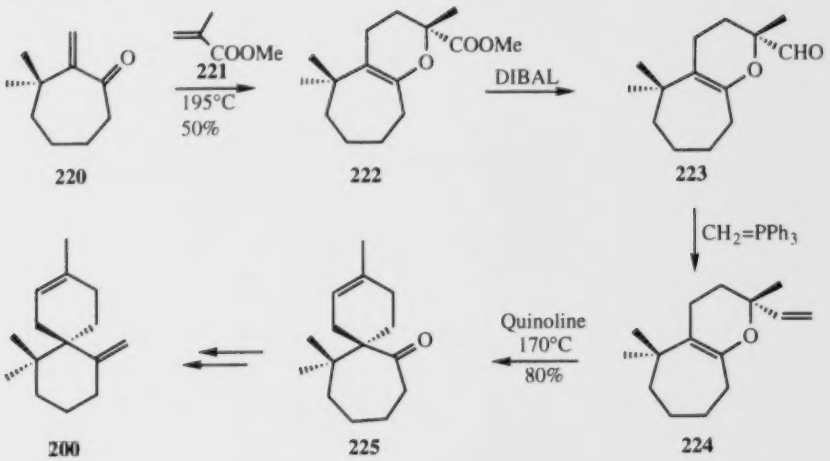
Scheme 35



Ireland developed a Diels-Alder condensation-Claisen rearrangement sequence for spiroannulation,[67] and this approach provided an efficient process for the total synthesis of (±)-β-chamigrene (Scheme 36).

The hetero Diels-Alder reaction of α-methylene ketone **220** with dienophile **221** gave adduct **222** (Scheme 36), which was then efficiently converted into the corresponding vinyl dihydropyran **224** via the aldehyde **223**. Rearrangement of allyl vinyl ether **224** in the presence of quinoline led to the desired spiroketone **225**, which was further converted to β-chamigrene **200** through ring contraction.

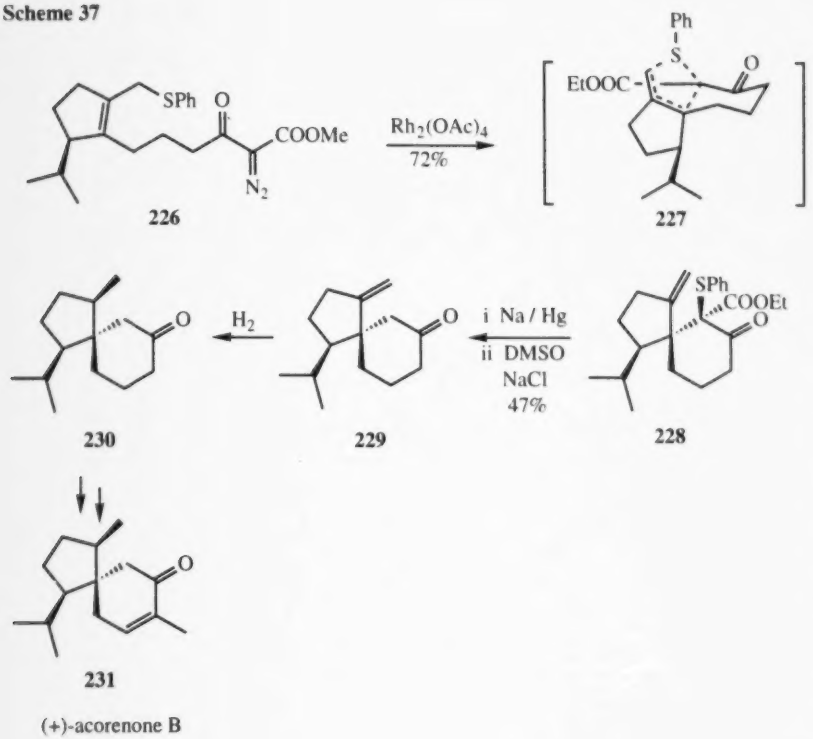
Scheme 36



A spiroannulation using a [2,3]-sigmatropic rearrangement was described recently by Kato and Kito.[68] The efficiency of this approach is illustrated in the synthesis of (+)-acorenone B, as shown in Scheme 37.

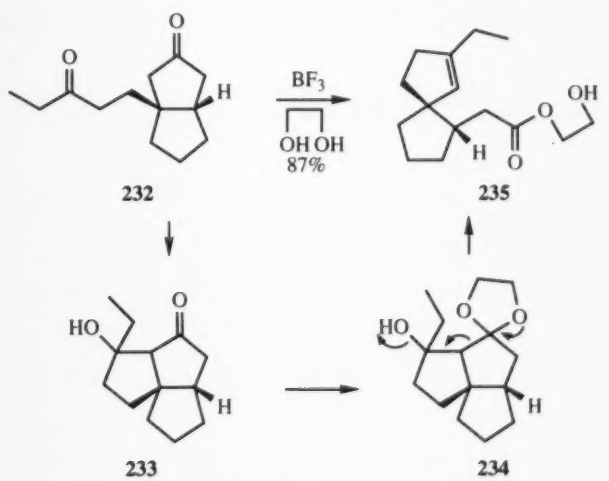
The [2,3]-sigmatropic rearrangement, via **227**, produced the spiroketone **228**. This spiroannulation proceeded in a stereoselective fashion to give **228** as the only product. The phenylthio and ethoxycarbonyl groups were removed by reductive desulfurization with sodium amalgam in MeOH and then decarboxylation with NaCl in aqueous DMSO. Hydrogenation of **229** proceeded exclusively from the face of the double bond opposite to the isopropyl group to give **230**, which is a known intermediate in previous syntheses of (+)-acorenone B (**231**).

Scheme 37



Sakai described a Lewis acid-catalyzed rearrangement of fused bicyclic diketones to spirocyclic compounds.[69]

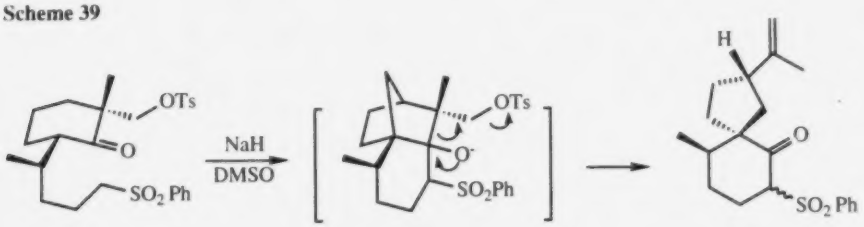
Scheme 38



The mechanism proposed is shown Scheme 38. Aldol **233**, formed by BF_3 catalyzed condensation, underwent fragmentation via acetal **234** to yield the spiro compound **235**.

Magnus reported a fragmentation process as a key step for the construction of the spiro[4,5]decane in (+)-hinesol[70] (Scheme 39).

Scheme 39

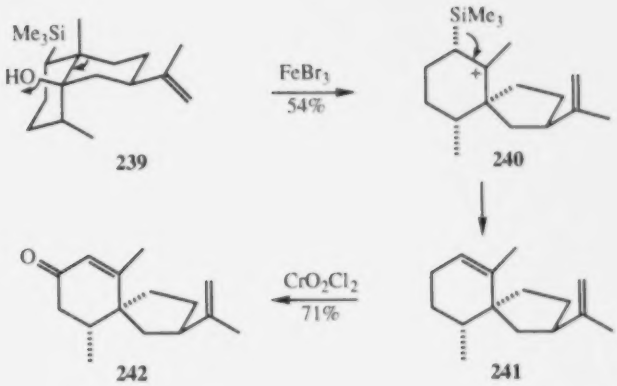


236 **237** **238**

Treatment of keto tosylate **236** with sodium hydride in DMSO resulted in formation of a β-ketosulfone **238** via fragmentation of intermediate **237**

A new method, involving silicon-promoted ring contraction,[71] was developed in the first enantioselective synthesis of the sesquiterpene (-)-solavetivone **242** (Scheme 40).

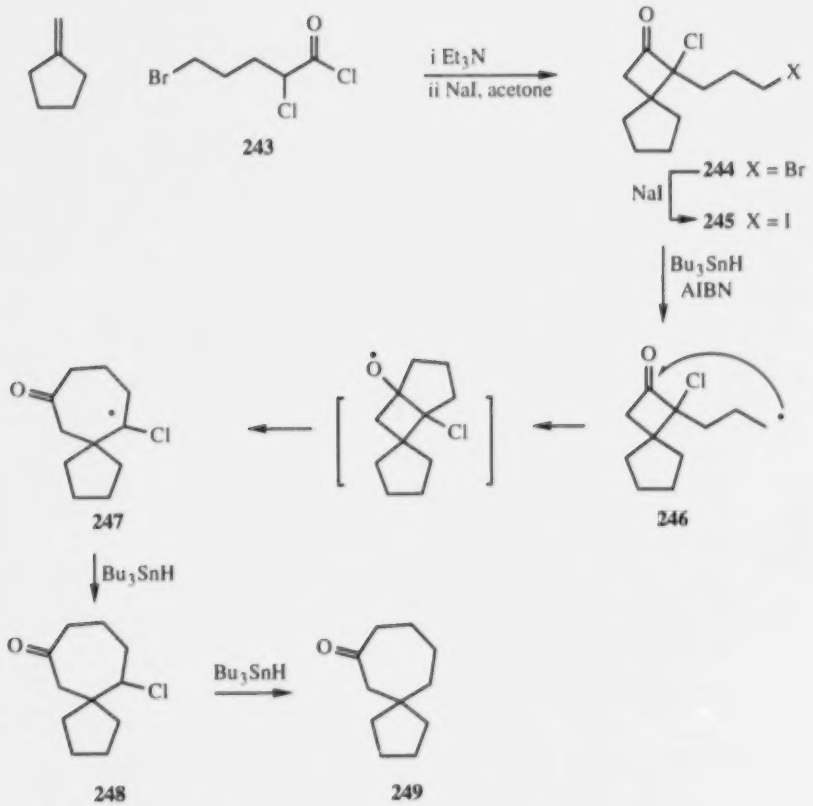
Scheme 40



Highly stereoselective ring contraction of **239** in the presence of $FeBr_3$ afforded the desired spiro compound **240**, which was then converted to (-)-solavetivone **242** by allylic oxidation.

Dowd described a radical-induced cyclobutanone ring expansion[72] as a new entry to seven- and eight-membered spiroannulated ring systems (Scheme 41). Regiospecific cycloaddition of methylenecyclopentane with the ketene derived from **243** yielded spirocyclobutanone **244** (Scheme 41). The adduct was transformed to the iodide **245**, which then underwent radical rearrangement to spiroketone **249**.

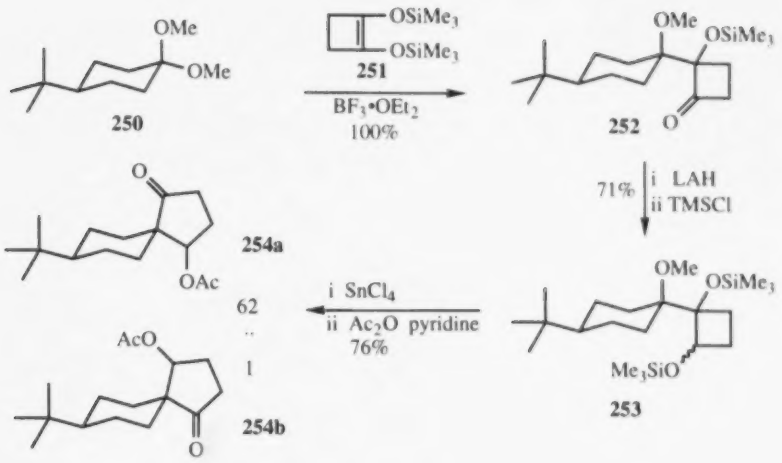
Scheme 41



The mechanism of this ring expansion was suggested to be as shown in Scheme 41. The initially formed radical **246**, closed onto the cyclobutanone carbonyl group to give an oxy radical. Regioselective opening of the oxy radical was assisted by the chlorine substituent. The chlorine was then reductively removed by tributyltin hydride.

Kuwajima developed a silicon-promoted ring expansion,[73] which provided a highly stereoselective synthesis of spirocyclic compounds (Scheme 42).

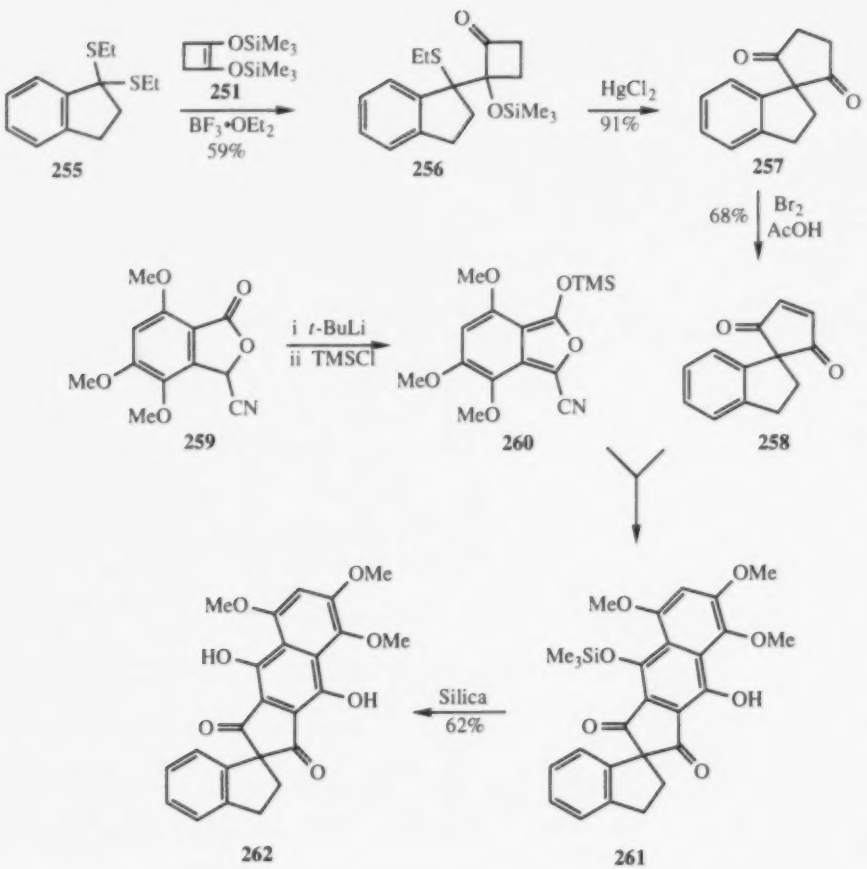
Scheme 42



Lewis acid-catalyzed aldol condensation afforded **252** as a single isomer. After reduction and silylation (**252→253**), the disilylated material (**253**) was treated with $SnCl_4$ to effect the 1,2 rearrangement. In this case a 62:1 mixture of **254a** and **254b** was obtained after acetylation. Evidently, the rearrangement occurred in a highly stereoselective fashion.

The application of this strategy led to a number of model studies related to fredericamycin A[74-76] and to two total syntheses.[16b,77] A modified Kuwajima reaction[74] was used by Bach, to make a novel spiro dienophile which underwent Diels-Alder reaction to give the quinone portion of fredericamycin A (Scheme 43).

Scheme 43



Reaction of thioacetal **255** with $BF_3 \cdot Et_2O$ and the bis(silylether) **251** afforded thioindenyl cyclobutanone **256**. The pinacol rearrangement of **256** to **257** (Kumajima reaction) was readily achieved by the action of the mild thiophile mercuric chloride, giving spirodiketone **257**. Preparation of dienophile **258** was completed by a bromination-dehydrobromination sequence (**257**→**258**). Then, Diels-Alder cycloaddition of endione **258** with the isobenzofuran **260**, generated *in situ*, afforded, after flash chromatography, the

desired spiroadduct **262** in 62% yield.

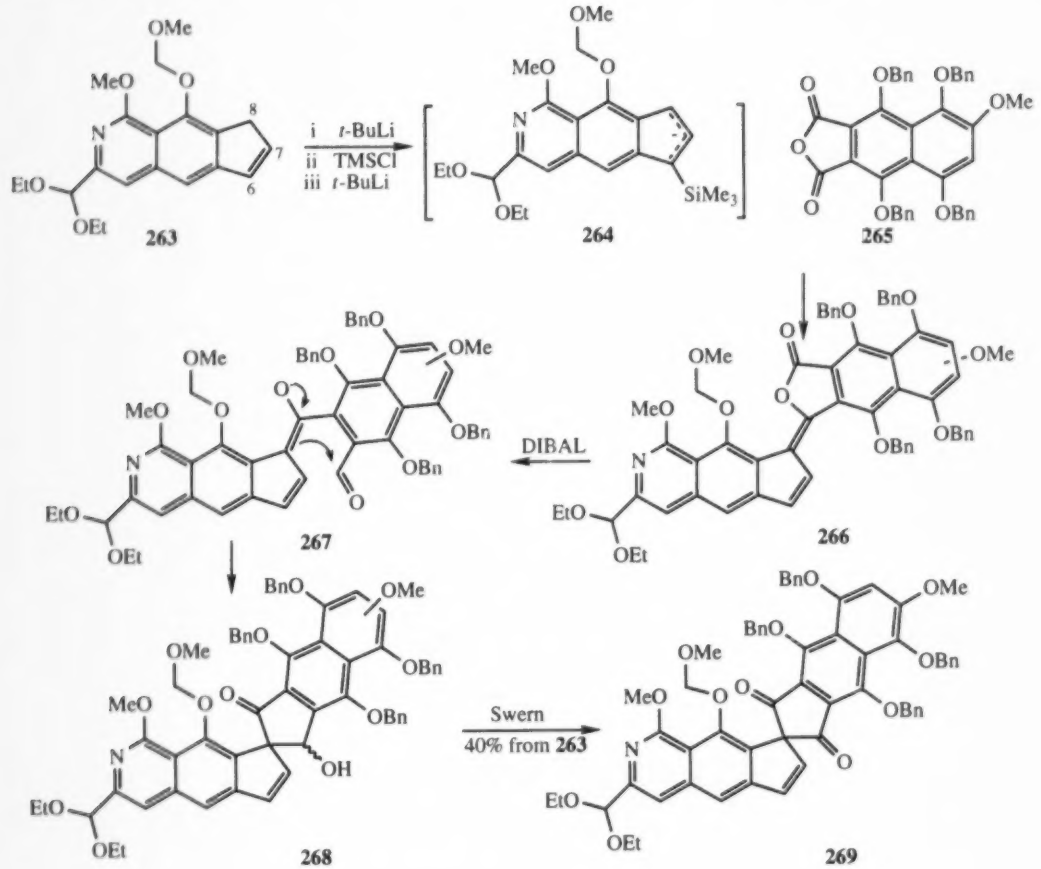
Total Synthesis of Fredericamycin A

The first total synthesis of fredericamycin A was completed by Kelly and co-workers.[78] Then our group reported another synthesis, based on 5-*exo* radical spirocyclization.[79] Over the last two years, three additional syntheses have appeared in literature.[16b,77,80]

In Kelly's synthesis, the spiro[4,4]nonane structure was tackled using a reductive aldol condensation, as shown in Scheme 44.

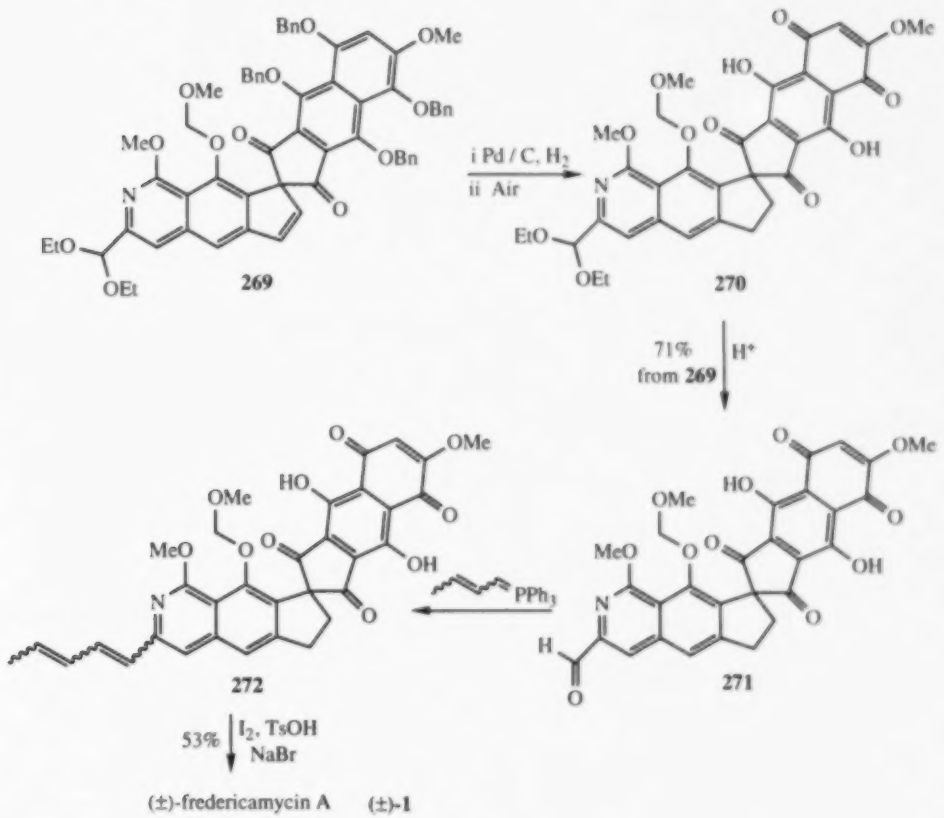
The TMS group was temporarily introduced in **263** to direct the coupling to the desired site by sterically blocking C-6. Conversion of **263** into silyl anion **264**, coupling with anhydride **265**, and lactonization, provided **266**. Reduction (DIBAL), followed by *in situ* aldol condensation, afforded **268**, as a mixture of four isomers. Oxidation of **268** furnished **269** in 40% overall yield from **263**.

Scheme 44



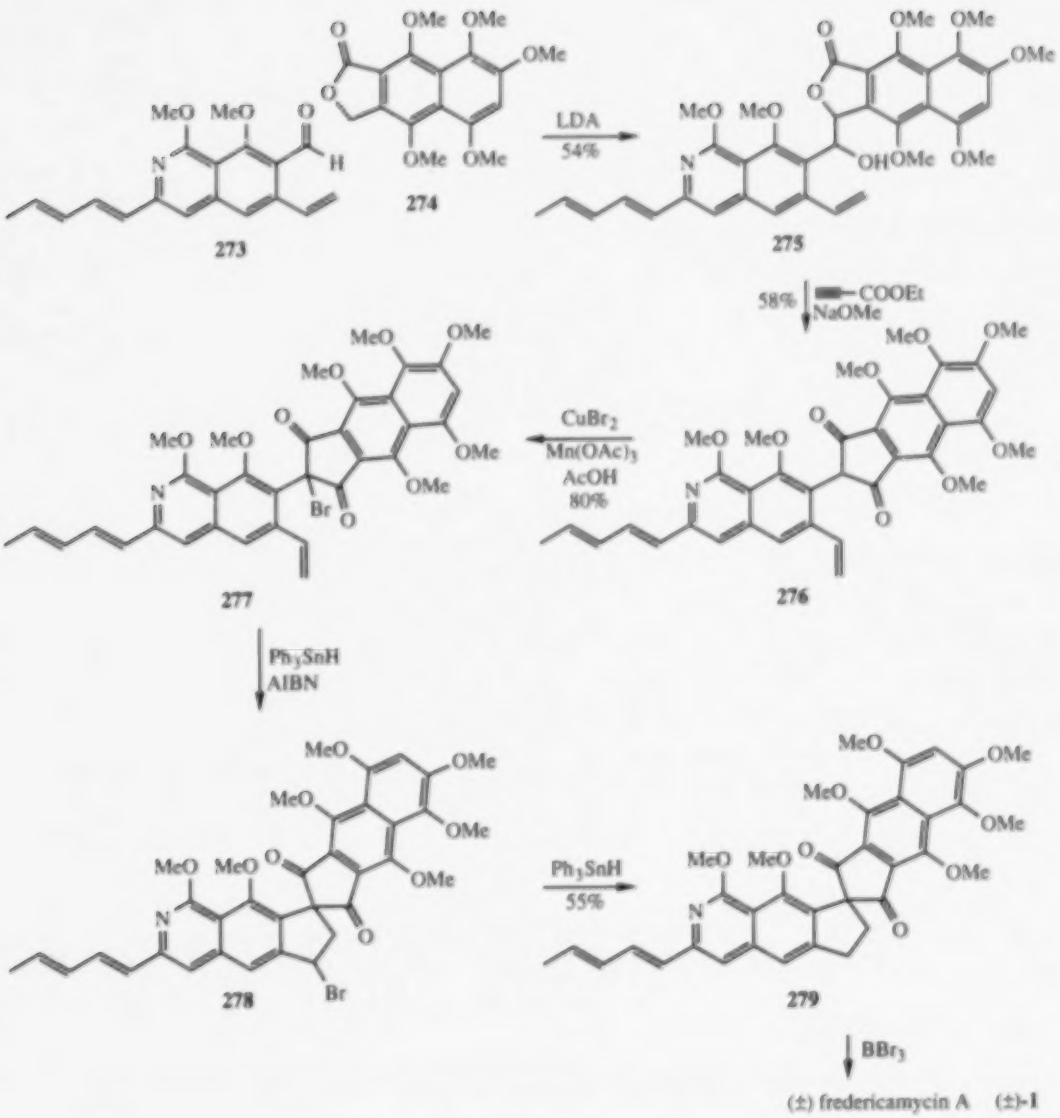
Hydrogenation of **269** over Pd/C (Scheme 45) served not only to saturate the indene double bond but also to remove the four benzyl protecting groups. Upon air oxidation, compound **270** was isolated in 78% yield. After hydrolysis of the benzylic acetal (**270**→**271**), the pentadienyl chain was built up rather inefficiently (20%) to produce **272** as a mixture of isomers. Finally, isomerization, double deprotection, and careful chromatographic separation of isomers gave a sample of synthetic fredericamycin A.

Scheme 45



Rama Rao and co-workers reported their synthesis which is based on 5-*endo* radical cyclization as a key step for construction of the spirocenter (Scheme 46).[80]

Scheme 46



Reaction between **273** and **274** in the presence of LDA, furnished **275**, which was rearranged to **276** by the action of sodium methoxide. The desired radical precursor was generated by treatment of **276** with $CuBr_2$, $Mn(OAc)_3$ and acetic acid. Radical cyclization under standard conditions with

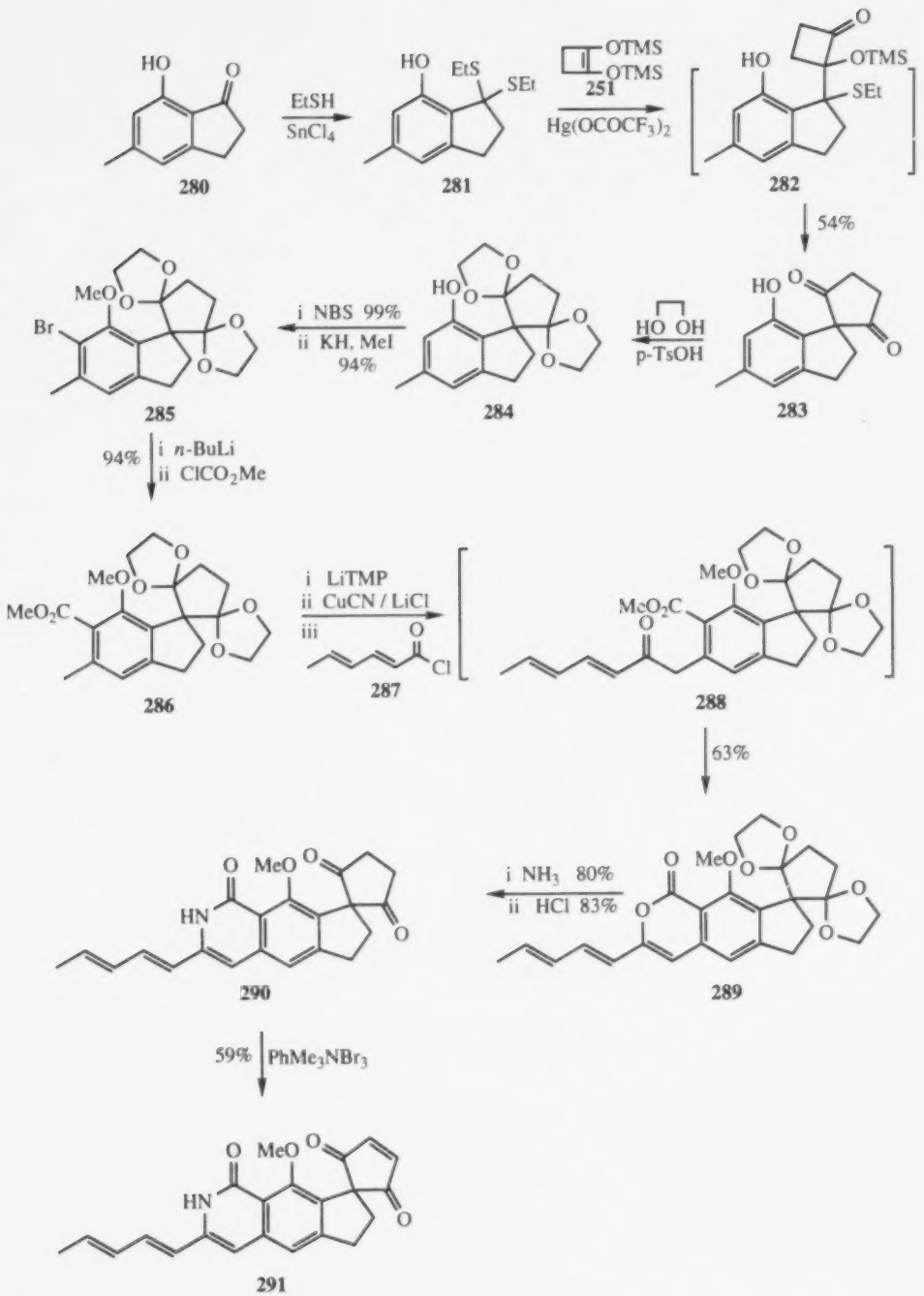
slow addition of triphenyltin hydride, followed by reductive elimination of the bromine atom from **278**, gave **279**, which is an intermediate in the synthesis reported from this laboratory. On demethylation, **279** afforded fredericamycin A. The radical cyclization of **277** to **278** is very unusual because it represents, at least formally, a 5-endo trigonal closure. Mechanistic information is not yet available for this step.

Recently, Bach described a very short and efficient total synthesis.[77] The spiro 1,3-dione was introduced utilizing a mild mercury-mediated pinacol rearrangement involving a 1,2-carbonyl migration (Kuwajima reaction) (Scheme 47).

The spirodione moiety was built up first. Dithioacetal **281**, prepared from **280**, was treated with mercuric trifluoroacetate in the presence of bis(silyl ether) **251** to give the acyl migration product **283**.

In order to introduce ring A, it is necessarily to activate the position *ortho* to the hydroxyl group. Towards this end, a methyl ester group was introduced by a number of standard operations (**283**→**284**→**285**→**286**). Ring A and the pentadienyl chain with the requisite *E,E* geometry was then built up in one operation. Acylation of the benzylic organocuprate derived from **286**, furnished **289**, after loss of methanol. Aminolysis of **289** with an excess of ammonia, followed by hydrolysis of the acetal protecting groups, afforded **290**. Dehydrogenation by a halogenation-

Scheme 47

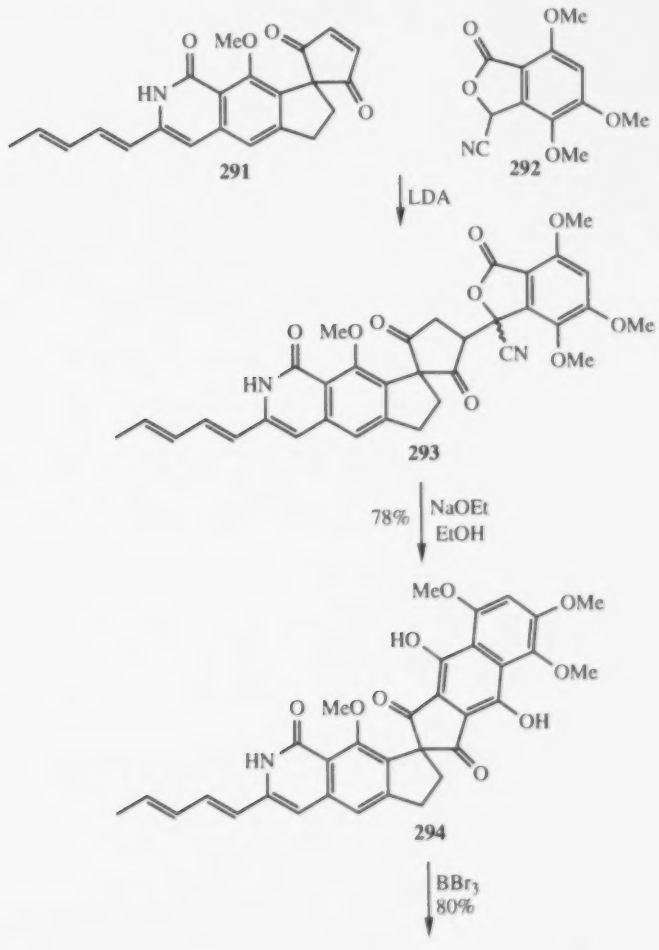


dehydrohalogenation sequence then provided the ABCD ring

system **291**.

Michael addition (**291→293**), followed by ring closure, gave the trimethyl ether of fredericamycin A (**294**) (Scheme 48). Demethylation and air oxidation completed the synthesis.

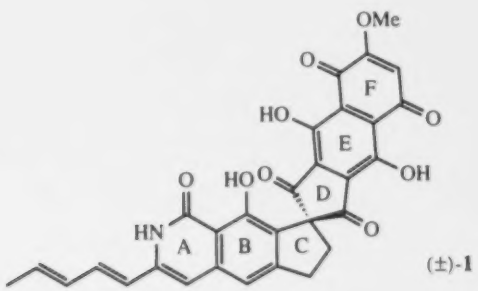
Scheme 48



II Results and Discussion

Part I Attempted synthesis of the quinone system of fredericamycin A

In the synthetic work on the total synthesis of fredericamycin A (**1**), which was carried out in this laboratory, the CD subunit was constructed by the general process of radical spirocyclization.[35]

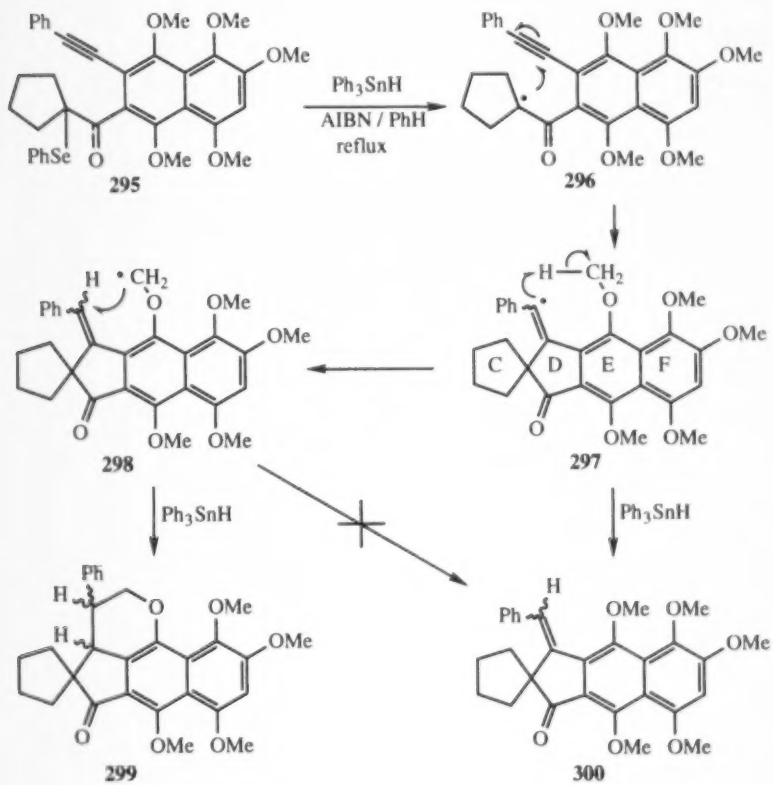


(±)-**1**

However, when this methodology was used to construct the CDEF ring system of fredericamycin A (Scheme 49),[81] the required final product **300** was isolated in only 48% yield (as a mixture of geometrical isomers). A very significant amount (41% yield) of a byproduct was formed by intramolecular hydrogen abstraction (**297**→**298**) followed by 6-*endo*-trigonal closure (**298**→**299**).[81] It was clear that the adjacent *peri* substituent forces the critical *O*-methyl group on ring E (see **297**) close to the vinyl radical. In principle, **298** could give **300**, by reaction with stannane. However, this appears not to have been the case because, when the reaction was done using triphenyltin deuteride, a deuterated analogue of **300**

was obtained in which the deuterium was located only (^{1}H NMR 400 MHz) on the vinyl carbon (PhCD= instead of PhCH=).

Scheme 49

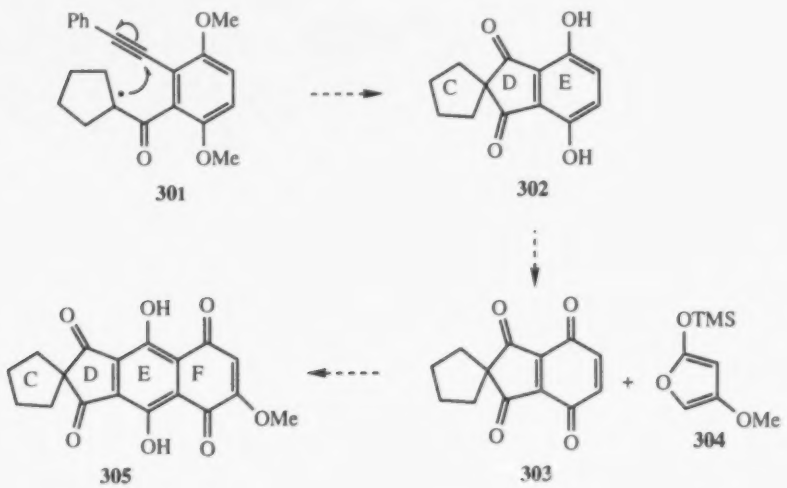


Efforts to improve the selectivity between the pathways leading to **300** and **299** by conducting the radical cyclization at room temperature with triphenyltin hydride in the presence of triethylborane and air[82] were fruitless. Thus, we were left with the task of avoiding or suppressing the undesired intramolecular hydrogen transfer.

Since the hydrogen transfer did not occur – at least to

any appreciable extent – with radicals of type **301** (see Scheme 50) ways were sought of building up the F-ring (*cf.* structure **1**) *after* the radical cyclization, and my first project was to test this approach (Scheme 50).

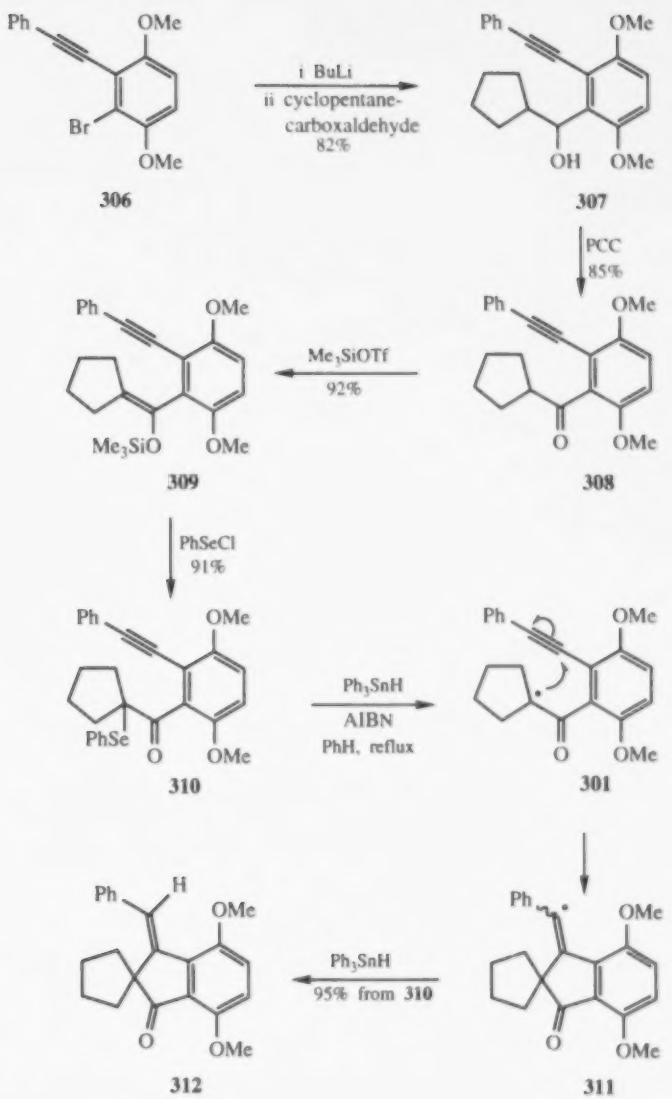
Scheme 50



Synthesis of the CDE ring system of fredericamycin A

Synthesis of the CDE ring system of fredericamycin A (**302**) was done without much difficulty: Bromide **306** was made by a known nine-step procedure[35] (Scheme 51). Halogen-metal exchange generated the required organolithium, and condensation with cyclopentanecarboxaldehyde[83] then gave alcohol **307**, which was oxidized to ketone **308** (Scheme 51) using PCC.

Scheme 51



However, when ketone **308** was phenylselenylated in the usual way, by treatment first with LDA followed by PhSeCl, a mixture of selenide **310** along with starting ketone **308** was obtained and the material could not be separated into its components. Therefore, a two-step procedure was tried.

Ketone **308** was first silylated and then converted into selenide **310** by the action of PhSeCl in the presence of triethylamine. Silyl enol ether **309** is unusual in that it can be chromatographed on silica gel without hydrolysis; most trimethylsilyl enol ethers are destroyed by contact with silica gel, but the present compound was not so sensitive in this respect, possibly because the silyl group is quite hindered, and so nucleophilic attack is slow.

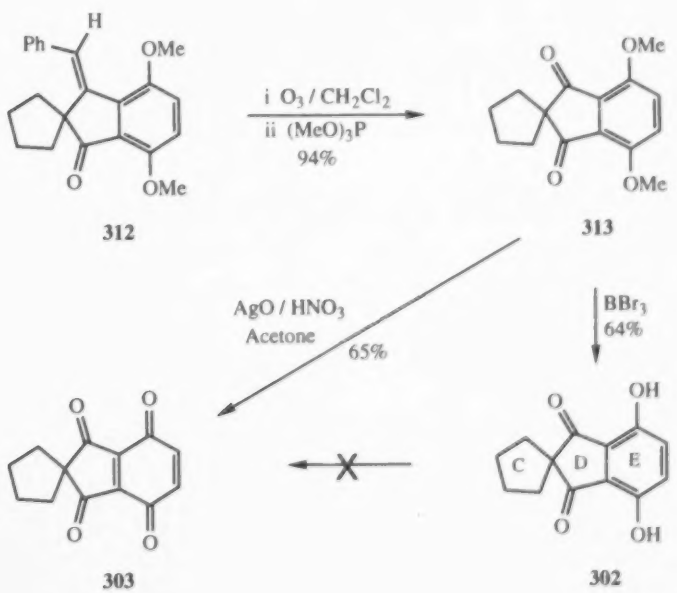
Standard thermal radical cyclization[35] (addition of triphenyltin hydride and AIBN to a refluxing benzene solution) gave only about 50% yield of cyclization product **312**. By carefully monitoring the reaction by TLC, it was found that the reaction was actually finished in 10 minutes and, when the product was isolated at this stage, olefin **312** was obtained in quantitative yield. The intermediate keto radical closed onto the triple bond in a 5-*exo* manner, producing the vinyl radical, which abstracted hydrogen from triphenyltin hydride to give only the *Z* alkene **312** (**311**→**312**).

Cleavage of the exocyclic double bond in **312** (Scheme 52) was best done by ozonolysis (94% yield) (**312**→**313**) rather than by vicinal hydroxylation (osmium tetroxide, *ca.* 77%) and glycol cleavage (periodic acid, *ca.* 63%). Demethylation under standard conditions[35] then completed the synthesis of the CDE ring system of fredericamycin A (**313**→**302**) (Scheme 52).

Attempts to construct ring F by Diels-Alder reaction

At this stage, we tried to build up ring F by the use of a Diels-Alder reaction. Towards this end, bisphenol **302** was converted into a dienophile by oxidation to the quinone level. Surprisingly bisphenol **302** was very difficult to oxidize to quinone **303**. A number of oxidation agents (cerium ammonium nitrate,[84] silver(II) oxide in acidic dioxane,[85] DDQ, and CrO_3 in acetic acid) were examined. In all cases, only complex mixtures were obtained. Therefore, we considered converting diketone **313** directly into dienophile **303**. Standard conditions [cerium ammonium nitrate or silver(II) oxide] resulted in complex mixtures but, eventually, we found that silver oxide and nitric acid in acetone effected the required transformation (Scheme 52).[86]

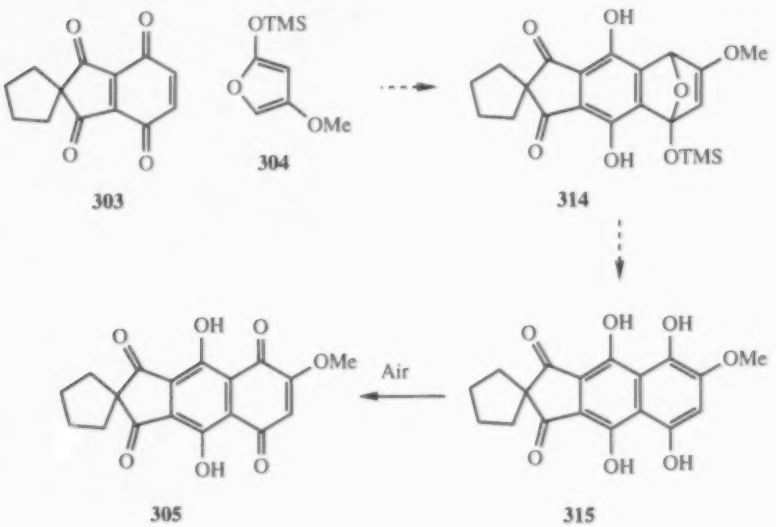
Scheme 52



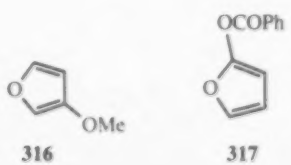
312 313 303 302

With dienophile **303** in hand, the Diels-Alder reaction with diene **304**[87] was examined. Diene **304** was chosen since, in principle, the reaction (Scheme 53) would give the desired CDEF ring system of fredericamycin A directly.

Scheme 53

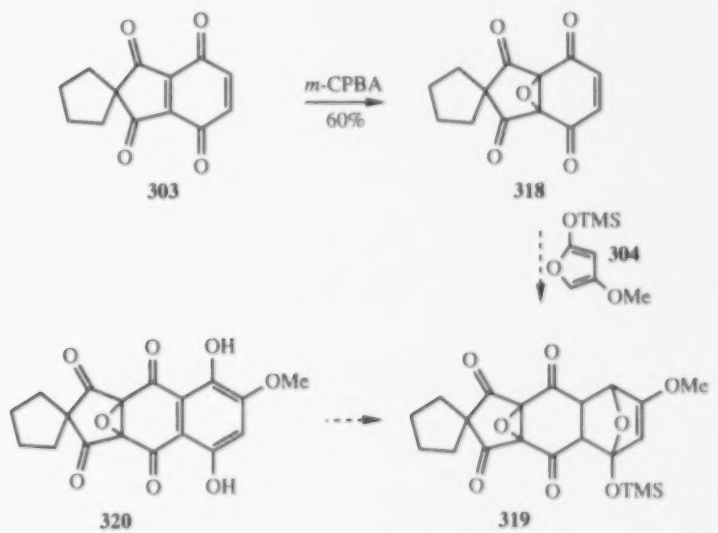


Quinone **303** was treated with diene **304** in dichloromethane,[78a] but after work up with acetic acid in methanol, only a complex mixture was obtained. When mild conditions[88] were used (refluxing benzene and work up with sodium acetate in acetic acid), surprisingly, quinone **303** was reduced to hydroquinone **302**.



Since **304** is a highly electron-rich diene, we wondered if less electron-rich dienes, such as **316** or **317**[89] would be better behaved. However, treatment of quinone **303** with **316** or **317** in a number of solvents (methylene chloride, acetic acid, benzene) afforded either complex mixtures or reduced hydroquinone **302**. Because the internal double bond in quinone **303** is more electron deficient, the Diels-Alder reaction might occur on this double bond first. In order to see if this possibility was the cause of our present difficulties, we next sought to block this double bond before attempting the Diels-Alder reaction.

Scheme 54

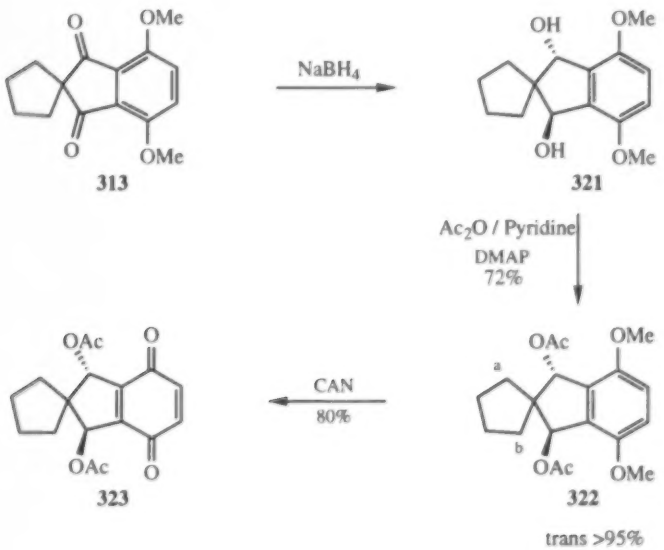


Epoxidation of quinone **303** with *m*-CPBA[90] gave the desired product **318** (Scheme 54). However, reaction of **318** with diene **304** again gave only a complex mixture and, at this

stage, we decided to make a less electron-deficient dienophile.

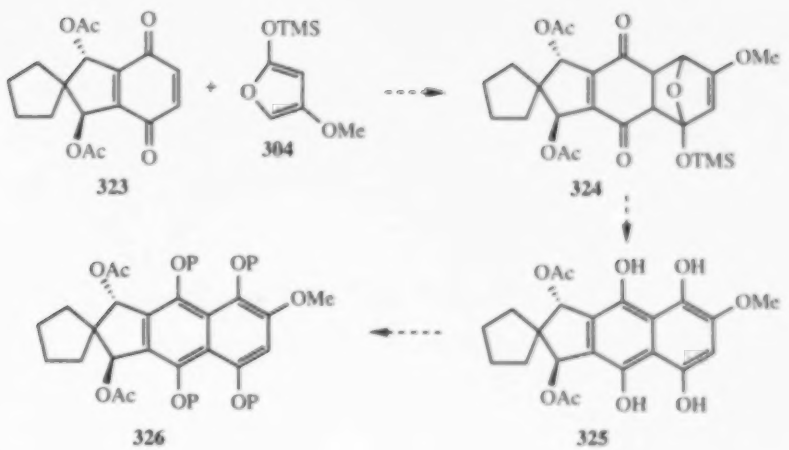
The carbonyl groups in **313** were reduced so as to afford a mixture of diols **321** which were then acetylated (**313**→**321**→**322**) to **322** (Scheme 55). Diacetates **322** were mainly trans isomer based on the fact that carbon a and b have the same chemical shifts on ^{13}C NMR.

Scheme 55



Oxidation [ammonium cerium(IV) nitrate] afforded the desired quinone **323**, which was almost exclusively (98%) the *trans* isomer shown. Treatment of quinone **323** with diene **304**

Scheme 56



under standard conditions[a] resulted in complex mixtures. The formation of unstable Diels-Alder adducts might be attributed to the sensitivity of the desired polyphenol system to aerial oxidation and, for this reason, we tried to protect, before workup, any unstable Diels-Alder adducts that might have been formed.[89] However, all our efforts at protecting the presumed adduct **325** (Scheme 56) by acetylation,[b] methylation,[c] or

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[a]Room temperature in CH_2Cl_2 (protecting group P in Scheme 56 = H) gave a complex mixture. Room temperature in PhH (P = H) gave a complex mixture. Reflux temperature in PhH (P = H) gave a complex mixture.

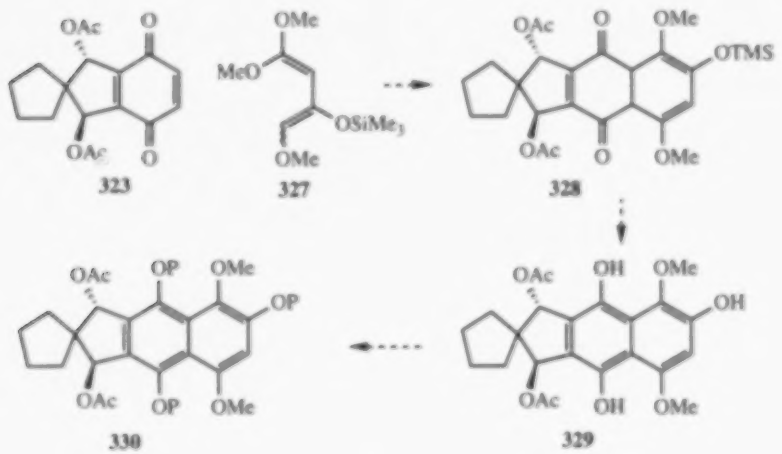
[b]Room temperature in CH_2Cl_2 (P = Ac), then Ac_2O and pyridine gave a complex mixture. Room temperature in CH_2Cl_2 (P = Ac), then Zn, Ac_2O and DMAP gave a complex mixture.

[c]Room temperature in CH_2Cl_2 (P = Me), then Me_2SO_4 and K_2CO_3 gave a complex mixture. Room temperature in CH_2Cl_2 (P = Me), then Me_2SO_4, NaOH, and $(Bu)_4NBr$ gave a complex mixture. Room temperature in CH_2Cl_2 (P = Me), then MeI and K_2CO_3 gave a complex mixture. Room temperature

benzylation[a] were fruitless, and we were unable to tell whether or not the adduct had actually formed.

Diene **327** was prepared according to the literature procedure.[88] This diene was chosen since the Diels-Alder adduct **329** (Scheme 57, P = protecting group) should be stable enough to be protected and isolated. However, under all the

Scheme 57



conditions[b] tried for Diels-Alder cycloaddition, only complex

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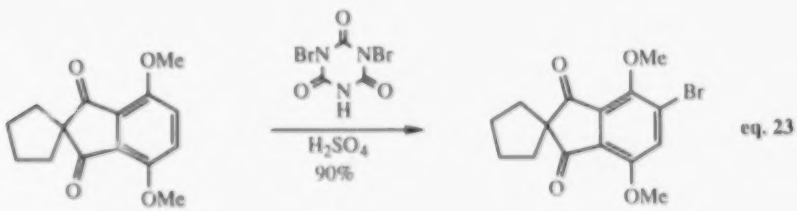
in CH_2Cl_2 (P = Me), then MeOTf gave a complex mixture.

[a]Room temperature in CH_2Cl_2 (P = Me), then BnBr and K_2CO_3 gave a complex mixture.

[b]Room temperature in CH_2Cl_2 (P in Scheme 57 = Me), then MeOTf gave a complex mixture. Room temperature in CH_2Cl_2 (P = Me), then MeOTf and K_2CO_3 gave a complex mixture. Room temperature in CH_2Cl_2 (P = Me), then Me_2SO_4, K_2CO_3 and MeOH gave a complex mixture. Room temperature in CH_2Cl_2 (P = Me), then Me_2SO_4, K_2CO_3 and acetone gave a complex mixture. Room temperature in CH_2Cl_2 (P = Ac), then Ac_2O, DMAP and pyridine gave a complex mixture.

mixtures were obtained.

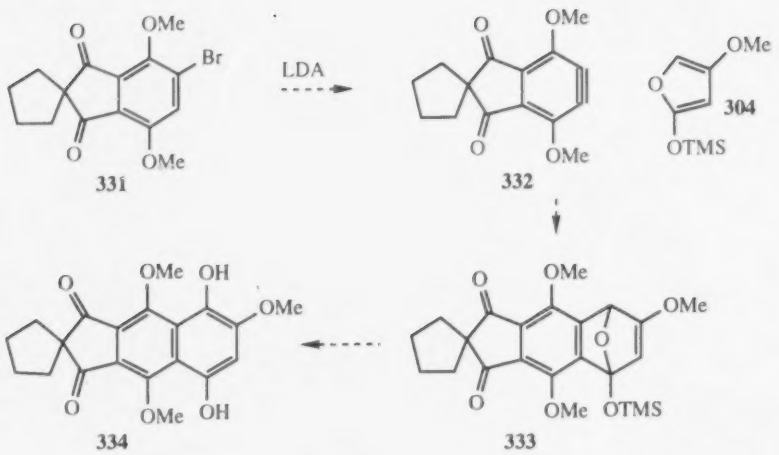
Use of a benzyne as a dienophile was considered next. The required precursor would be bromide **331**. Bromination of diketone **313** was quite troublesome. A number of common bromination agents[91] such as pyridinium bromide perbromide, bromine in acetic acid, bromine in pyridine, and bromine in refluxing carbon tetrachloride with iron as a catalyst were all tried.[91] Under all of these conditions only diketone **313** was isolated. Apparently, the two electron-withdrawing carbonyl groups in **313** strongly decreased the reactivity of the aromatic ring towards electrophiles. Nevertheless, we were able to convert diketone **313** into bromide **331** (eq. 23) using a very powerful bromination agent, dibromoisocyanuric acid.[92]



313 331 eq. 23

Treatment of this bromide (**331**) with LDA in the presence of diene **304** did not give the desired Diels-Alder adduct (Scheme 58),[93] and only the starting bromide **331** was isolated. Evidently benzyne **332** was not formed.

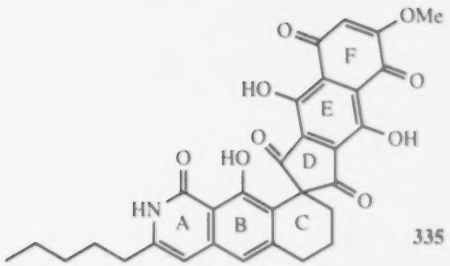
Scheme 58



At this point, the total synthesis of fredericamycin A[78] was successfully completed in our group and the undesired intramolecular hydrogen transfer was not observed under the conditions used for the crucial radical spirocyclization. Consequently, we decided to stop work on our attempts to make the CDEF ring system of fredericamycin A. Such efforts to avoid the problem of intramolecular hydrogen transfer were clearly no longer warranted.

Part II Synthesis of tetrahydrohomofredericamycin A

The second project involved synthesis of an analog (**335**) of fredericamycin A in which (i) the C-ring is expanded from a five-membered to a six-membered ring, and (ii) the pentadienyl side chain has been saturated.



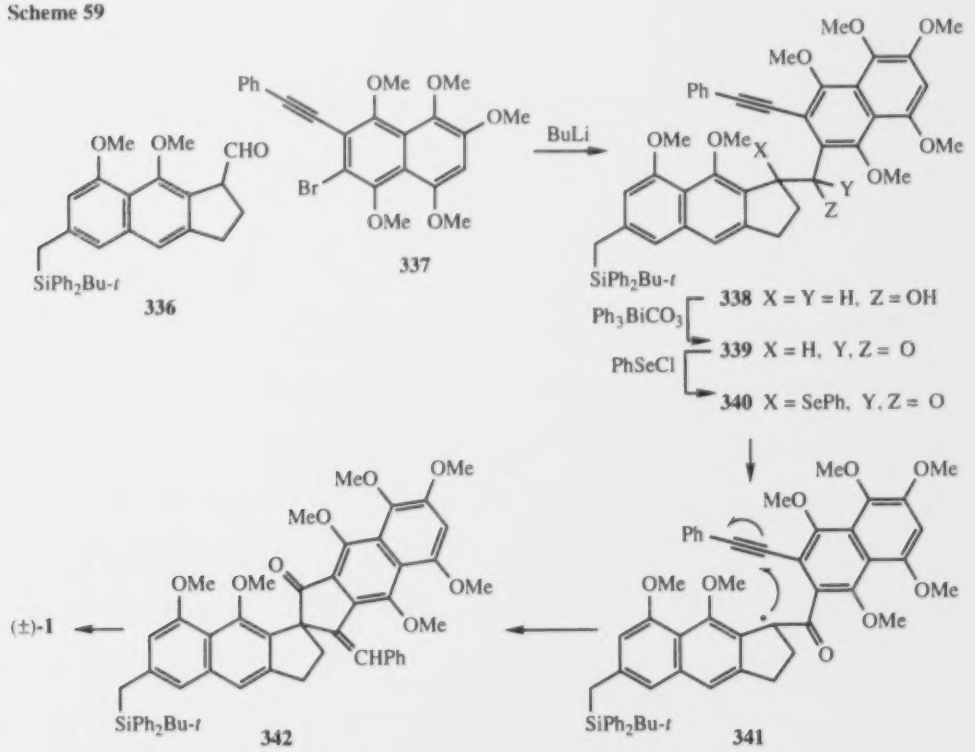
335

Our reasons for undertaking the synthesis of such an analogue were as follows: Expansion of the C-ring from five to six carbons would alter the angle between the two flat plates that make up the structure of fredericamycin A and any electronic interaction[5] between the components would accordingly be changed. As the spiro system of the natural product is one of its characteristic and unusual (among antitumor agents) features, the influence of such changes on biological activity is an important consideration if fredericamycin is to serve as a lead compound in the design of other antitumor agents. The ring expansion would also have the effect of making the molecule a little more flexible, and might serve to make it fit more easily into a receptor site. Saturation of the pentadienyl side chain was selected merely to simplify the synthetic problem, as controlling the double bond geometry is not a trivial task, as other members of the fredericamycin group in this laboratory found during the synthesis of the natural product. The status – saturated or unsaturated – of the side chain is not expected to alter the biological activity significantly, as it does not do so in the case of fredericamycin itself.[94]

Attempted spirocyclization of α- and γ-keto radicals

At the time I started this project, fredericamycin A had been synthesized in our group via the radical spirocyclization shown in Scheme 59.

Scheme 59



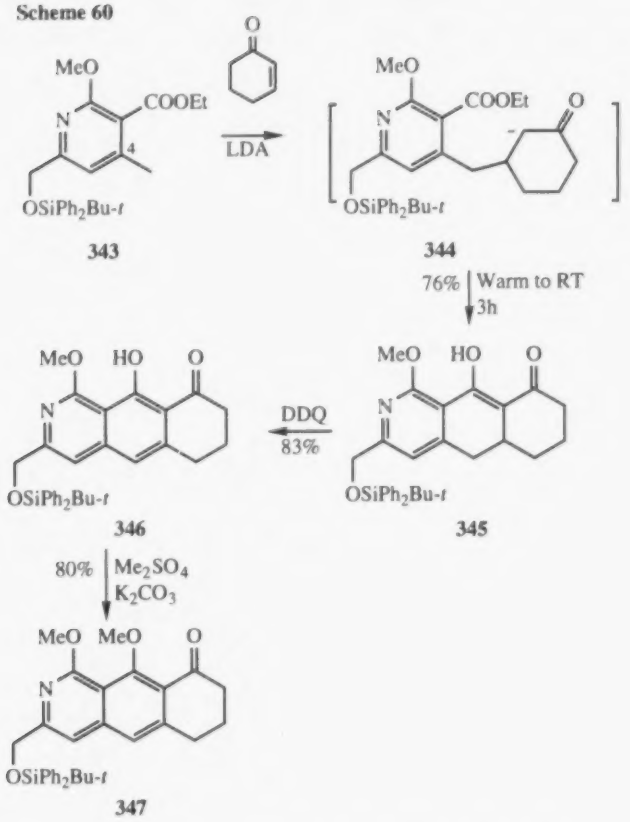
The radical precursor, in the form of α-keto selenide **340**, was generated from the corresponding ketone **339**, itself assembled from two components, the bottom piece aldehyde **336** and the top piece bromide **337**. Radical spirocyclization in a 5-*exo* manner gave ketone **342**, which was subsequently elaborated to fredericamycin A. This route served as the initial guide to our plans for making analogue **335**, although,

in the event, a different approach had to be adopted. By comparing analog **335** and fredericamycin A, it is easy to see that if ring C of the bottom piece aldehyde **336** is changed into a six-membered ring, then the route used in the synthesis of fredericamycin A should be applicable to the analog.

Synthesis of the first ABC subunit

The route used in the synthesis of fredericamycin A was adapted to make a ketone (**347**) with a six-membered C-ring. We started with the methyl pyridine ester **343** (Scheme 60), which was readily made[78] in six steps from commercially available starting materials. The methyl group at C-4 of **343** was easily deprotonated with LDA and the resulting carbanion underwent conjugate addition to cyclohexenone (**343→344**) (61%). Base-catalyzed cyclization (NaH, trace EtOH) gave a β-diketone (57%, which exists largely in its enolized form **345**, as clearly shown by ^{1}H NMR and ^{13}C NMR spectra. It was found that intermediate **344** need not be isolated. Upon warming the reaction mixture from the conjugate addition to room temperature, **345** was formed in 76% yield (**343→345**). The next step, dehydrogenation with DDQ (**345→346**), must be monitored carefully by TLC, since naphthol **346** is very easily

Scheme 60



dehydrogenated further to afford a product in which ring C has been aromatized. In contrast to the synthesis of the five-membered ring-C aldehyde **336**, which was used in the synthesis of fredericamycin, no methylation of **346** occurred under the Mitsunobu conditions (Ph_3P, DEAD, MeOH)[79] that had worked well in the route to **336**. Naphthol **346** was, however, easily methylated under standard conditions with dimethyl sulfate and potassium carbonate in refluxing acetone (**346**→**347**).

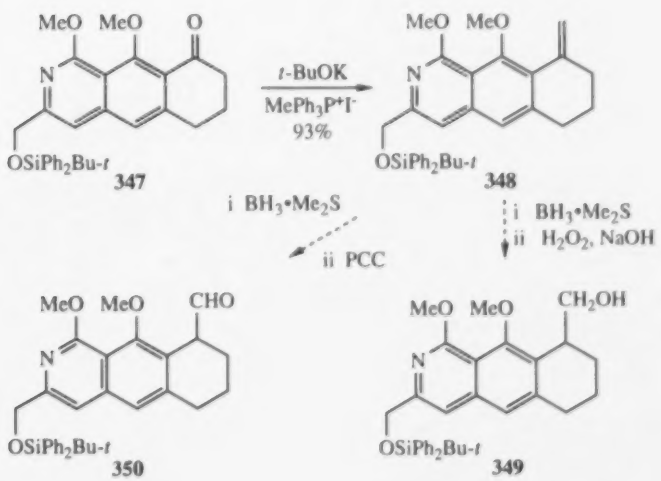
While the methylation was easily accomplished, homologation of the resulting ketone **347** to aldehyde **350**

(see Scheme 61) proved to be a very difficult task. We first tried to use the approach that had been successful in the fredericamycin A synthesis.

Wittig-hydroboration approach

To this end, chain extension of ketone **347** with methylene triphenylphosphorane gave **348** (Scheme 61). However, treatment of **348** with borane•dimethyl sulfide complex, followed by oxidation with alkaline hydrogen peroxide or PCC[95] did not give alcohol **349**, or aldehyde **350**, respectively. Alkene **348** is very unstable and extremely easy to isomerize, but we do not know if these characteristics are responsible for the formation of complex mixtures in our attempts at hydroboration and oxidation.

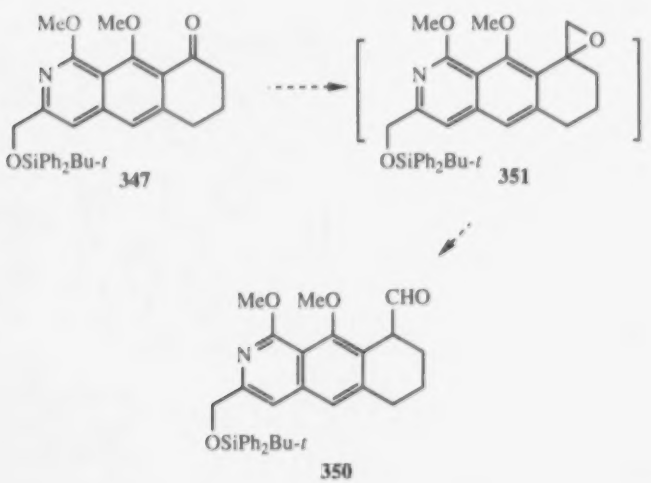
Scheme 61



Sulfur ylide approach

Use of a sulfur ylide was considered next, since it should give the desired aldehyde **350** in one step from ketone **347** (Scheme 62).

Scheme 62



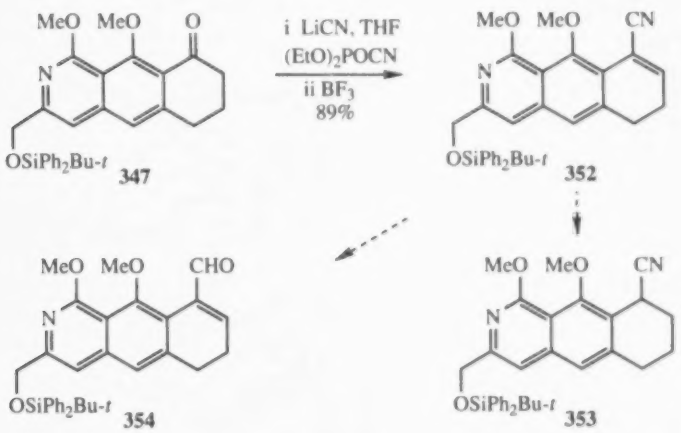
Treatment of ketone **347** with Me_3SOI[96] or Me_3SI[97] in the presence of dimsyl anion (from NaH and DMSO) led to complete recovery of ketone **347**. Possibly, the ketone is enolized under the reaction conditions, and so it is not attacked by the methylenating reagent.

Conjugate nitrile approach

Addition of cyanide was tried next in our attempts to homologate ketone **347** (Scheme 63). The α,β-unsaturated nitrile **352** was made without much difficulty, by a standard procedure.[98] However, reduction of the α,β-unsaturated

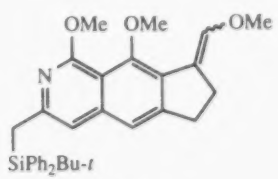
nitrile **352** to the corresponding aldehyde[99] **354**[a] or to the saturated nitrile[100-102] **353**[b] under several conditions was unsuccessful.

Scheme 63



Enol ether approach

From the work on the synthesis of fredericamycin A, we knew that enol ethers **355** cannot be hydrolyzed to the corresponding aldehyde without damaging other parts of the



355

molecule, but it was clear that if some more easily

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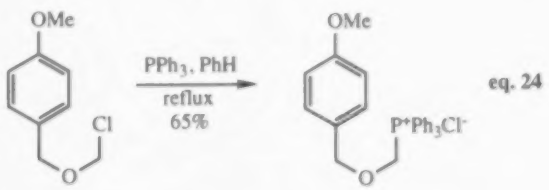
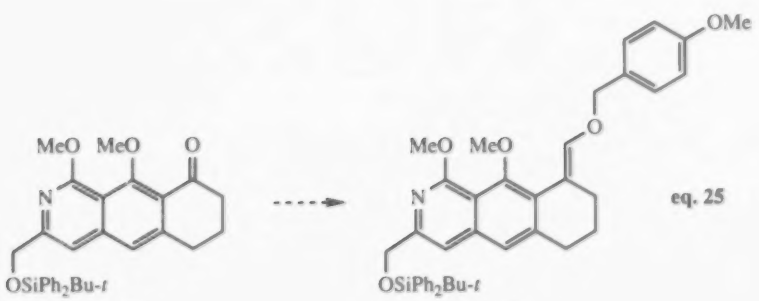
[a] Pd/C, H_2 gave recovered starting material. Mg and MeOH gave a complex mixture. $CrSO_4$ gave recovered starting material.

hydrolyzed enol ether were made, it should be possible to obtain the desired aldehyde in the present case. One approach was to make **358** (eq. 25), which should be obtained from the new Wittig reagent derived from **357**. Chloride **356**[103] was treated with triphenylphosphine in refluxing benzene to generate the phosphonium salt **357**. Reaction of ketone **347** with the derived Wittig reagent (eq. 25) afforded either a complex mixture (BuLi as the base) or led to recovery of starting material (*t*-BuOK as the base).



356 **357** eq. 24

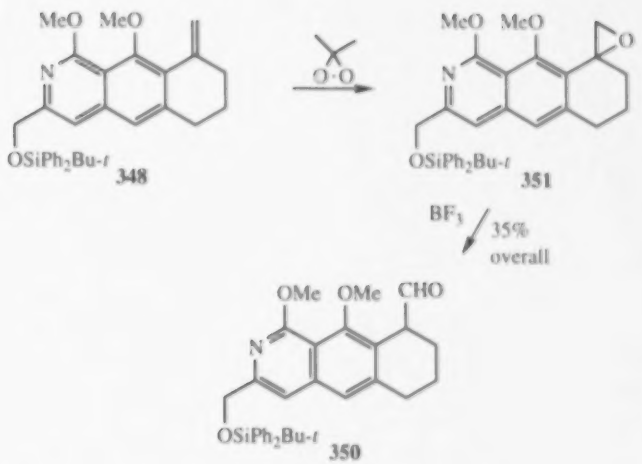


347 **358** eq. 25

Rearrangement of an epoxide

Rearrangement of an epoxide to an aldehyde[104] is a well-established route to aldehydes, and we decided to explore this approach (Scheme 64).

Scheme 64



As stated earlier, olefin **348** is very unstable and should be used immediately after isolation. The freshly-made

Table I Epoxidation of olefin **348**.

Entry	Conditions	Results
1	*m*-CPBA	Complex mixture
2	*m*-CPBA, $NaHCO_3$	10% epoxide **351**
3	MeCN, H_2O_2, $KHCO_3$	Starting material or complex mixture
4	PhCN, H_2O_2, $KHCO_3$	Complex mixture
5	Dimethyldioxirane, -20 °C	70% epoxide **351**
6	Dimethyldioxirane, -78 °C	10% aldehyde **350** and 16% allylic alcohol

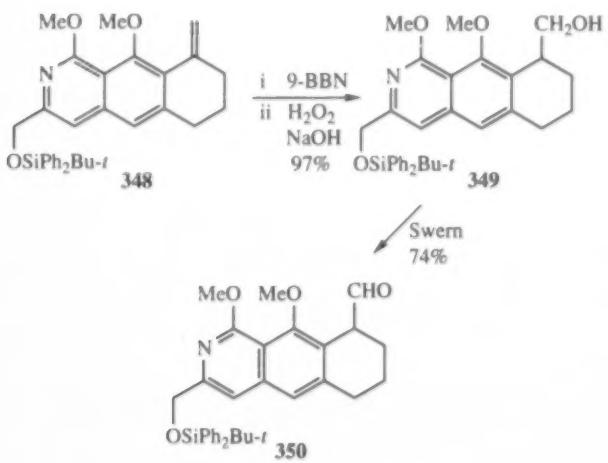
olefin was treated with a variety of epoxidation agents as shown in Table I. Standard epoxidation conditions[105] (entries

1-4) gave either complex mixtures, or afforded a very low yield of epoxide; however, epoxidation with dimethyldioxirane[105c] (entry 5) gave acceptable yields of epoxide **351** and thence aldehyde **350** (Scheme 64). Unfortunately, this reaction was difficult to repeat. As large quantities of aldehyde **350** were needed to carry on the total synthesis, this route did not prove to be useful.

9-BBN approach

As so many other potential methods for homologation of ketone **347** were unsuccessful, it was worthwhile to see if a

Scheme 65



different borane reagent could be used to hydroborate olefin **348**. To our delight, when freshly made alkene **348** was treated with 9-BBN, followed by oxidation with alkaline hydrogen peroxide, the desired alcohol **349** was obtained in

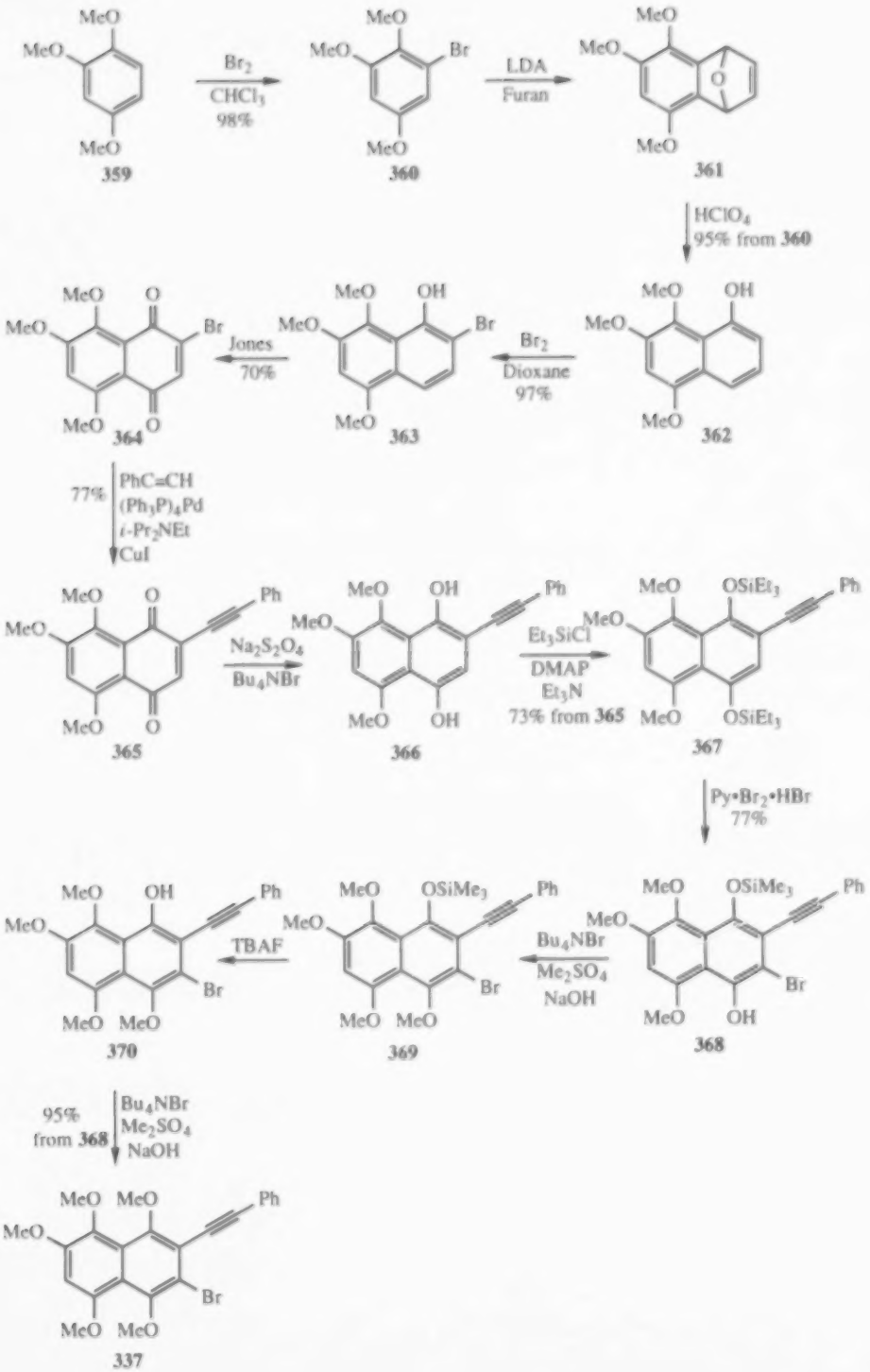
high yield (Scheme 65). Swern oxidation then generated aldehyde **350**, and so, at long last, we had the required bottom piece aldehyde **350** in hand.

Linking of the EF and the first ABC subunit, and attempts to generate the radical precursor (α-keto selenide)

Bromide **337**[81] had been made in the synthesis of fredericamycin A by a 12-step procedure (Scheme 66), and we quickly repeated this sequence.

With both the bottom piece aldehyde **350** and the top piece naphthalene **337** in hand, the next step was to link the two subunits together. However, in many of our early attempts, this reaction gave only a low yield (20%) of the desired coupled product **371** (as a mixture of isomers) (Scheme 67). Eventually, we discovered that there are two factors which affect the yield:

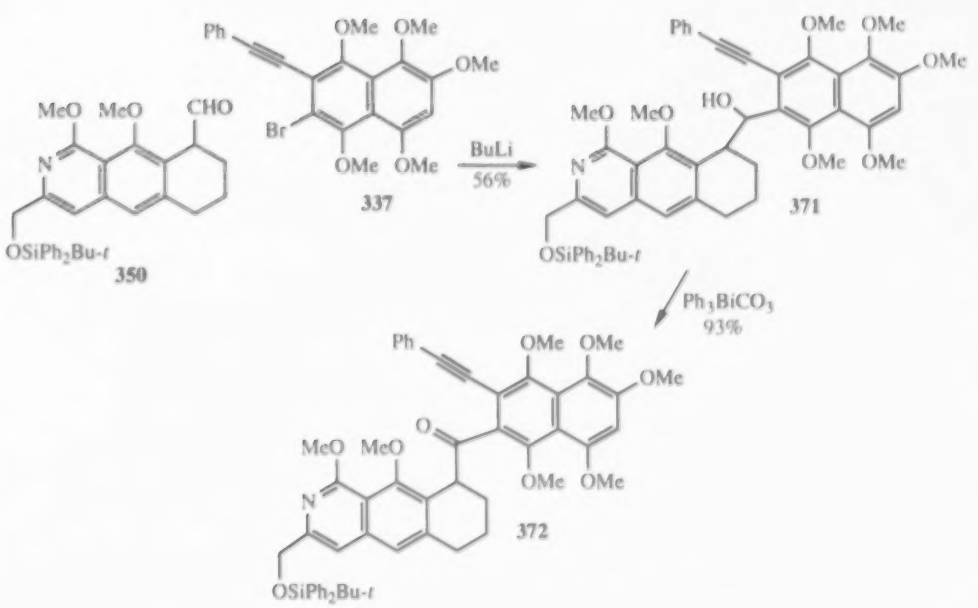
Scheme 66


MeO
MeO
MeO
359
Br2
CHCl3
98%
Br
360
LDA
Furan
O
361
HClO4
95% from 360
OH
362
Br2
Dioxane
97%
363
Jones
70%
O
364
77%
PhC≡CH
(Ph3P)4Pd
i-Pr2NEt
CuI
Ph
365
Na2S2O4
Bu4NBr
366
Et3SiCl
DMAP
Et3N
73% from 365
OSiEt3
367
Py•Br2•HBr
77%
OSiMe3
368
Bu4NBr
Me2SO4
NaOH
369
TBAF
370
95%
from 368
337

First, traces of ethyl acetate in bromide **337** will significantly affect the coupling yield and the best way to avoid this problem is to crush the solid bromide **337** into a very fine powder and keep it under diffusion pump vacuum for 24 hours.

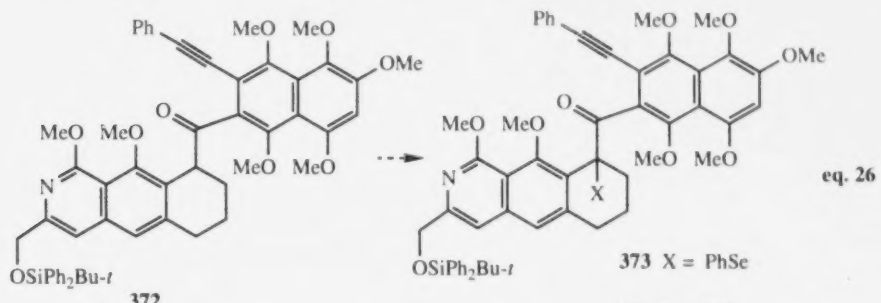
Second, the reaction has to be done on a relatively large scale (>100 mg) in order to get good yields.

Scheme 67



Oxidation of the coupled alcohols to ketone **372** was accomplished efficiently with triphenylbismuth carbonate[106] (**371→372**). From this point, introduction of a benzeneseleno group would give the starting material **373** for radical spirocyclization. However, this radical processes

could not be tried since all attempts at phenylselenenylation, or related transformations gave unpromising results (eq. 26).



When the conditions used in the synthesis of the corresponding selenide with a five-membered C-ring were tried, ketone **372** was completely recovered.[a] Longer reaction periods led to a complex mixture.[b] Phenylseleno agents with better leaving groups[107] were also examined[c], but again, no selenation was observed. At this point, we suspected that deprotonation with lithium diisopropylamide and butyllithium did not occur. To check this point, ketone **372** was treated with lithium diisopropylamide and butyllithium, and the mixture was worked up with deuterated methanol. Ketone **372** was recovered without any deuterium incorporation. This

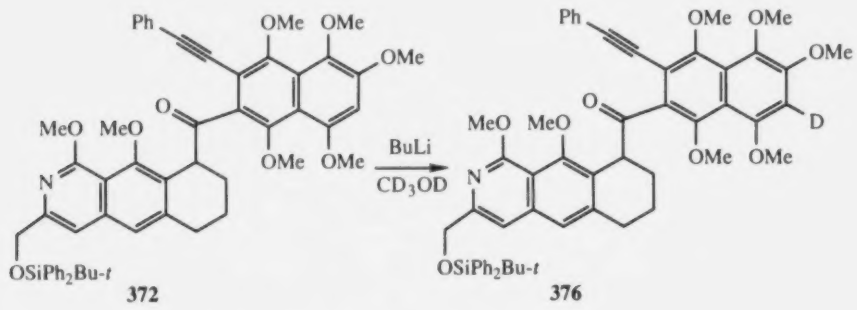
---

[a]LDA, BuLi, PhSeCl 1 h at -78 °C.

[b]LDA, BuLi, PhSeCl 1 h at -78 °C, then warm to room temperature for 12 h.

[c]LDA, BuLi, PhSeBr at -78 °C gave recovered starting material. LDA, BuLi and $PhSeSe^{+}MePhBF_4^{-}$ gave recovered starting material.

result implied that deprotonation had not occurred. We decided to use a higher temperature.[a] Surprisingly, the corresponding enol was formed. Apparently, deprotonation did occur this time, but the enolate is not reactive enough to combine with PhSeCl or PhSeBr to give the desired selenide **373**. We also tried to use other bases,[b] but without any success. In the case of BuLi, deprotonation occurred at ring F instead of at the α position, as shown in eq. 27.



372 **376** eq. 27

$PhSeNEt_2$[108] is good reagent for selenation of aldehydes, but exposure of ketone **372** to this reagent led only to recovered starting material. Finally, ketone **372** was treated with PhSeCl in ethyl acetate,[109] a complex mixture was formed.

Other groups which can be used as radical precursors, such as -Br [$CuBr_2$, $Mn(OAc)_3$, HOAc] **375**[79] and -SPh (KHMDS, PhSSPh, HMPA),[110] were examined (eq. 26, X = Br or PhS), but

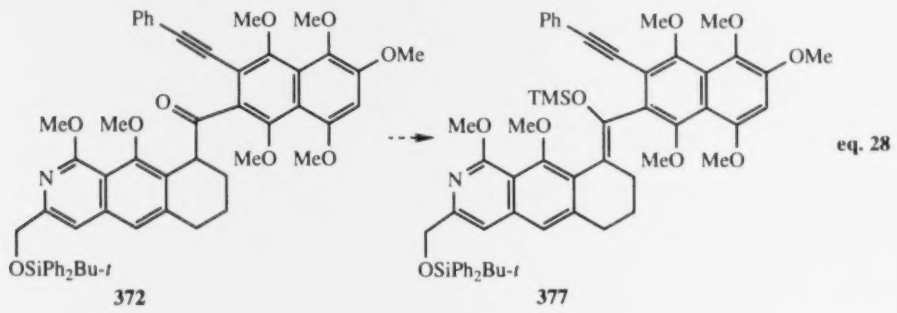
---

[a]LDA, BuLi, PhSeCl, HMPA, 0 °C gave enol. LDA, BuLi, PhSeBr, 0 °C gave enol and starting material.

[b]KH, PhSeCl, and 18-crown-6 gave a complex mixture. BuLi and PhSeCl gave a complex mixture.

in both cases, ketone **372** was recovered.

Since silyl enol ethers can be converted easily into selenides, we tried to make the silyl enol ether **377** from ketone **372** (eq. 28). However, no trace of silyl enol ether **377** could be detected under all the conditions that we examined.[a]



Synthesis of the second ABC subunit and attempts to generate selenide 379

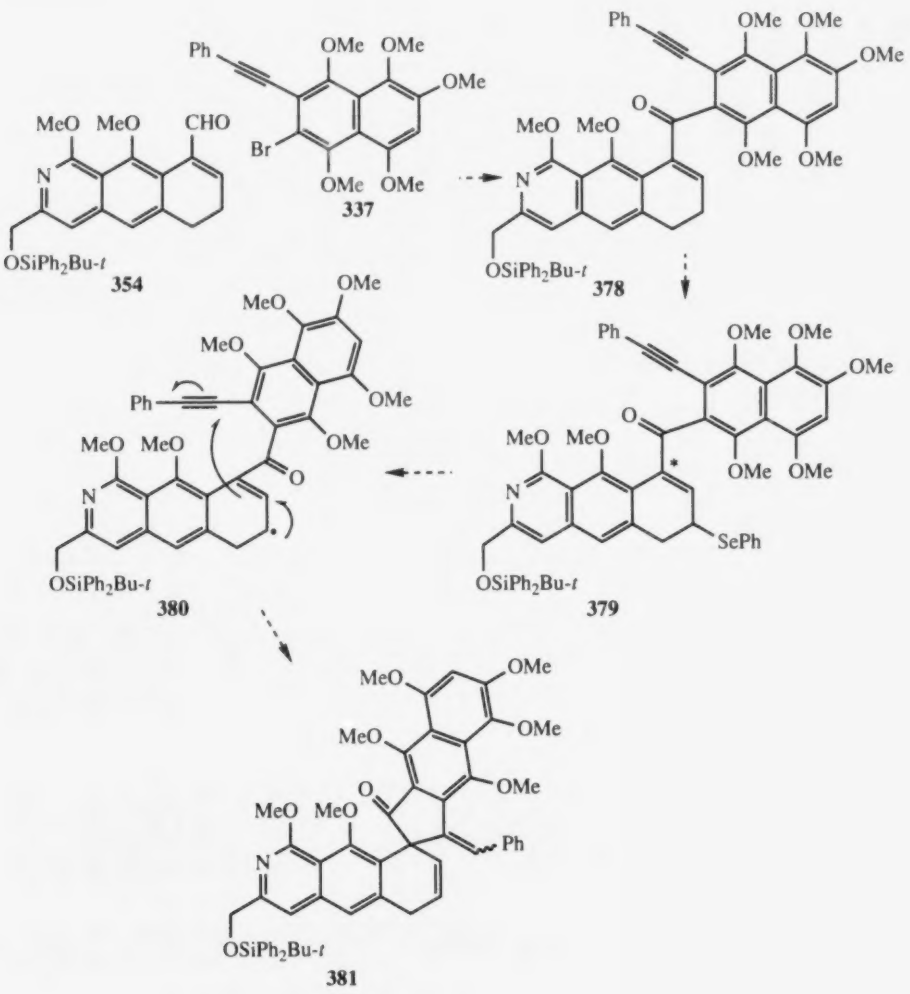
As discussed above, all attempts to make the α-keto selenide **373** were unpromising. Therefore, we considered the possibility of inserting a double bond between the carbonyl and PhSe groups, that is, we decided to make the γ-keto selenide **379**. This would involve placing the phenylseleno group some distance from the sterically congested quaternary carbon (see **379**, starred atom). If the selenide could be

---

[a]TMSOTf and Et_3N gave recovered starting material. TMSOTf and 2,6-lutidine gave recovered starting material. KH, TMSCl, and Et_3N gave a complex mixture. BuLi, LDA, TMSCl, and Et_3N gave recovered starting material.

made, it would lead to the desired spiro compounds **381** via radical cyclization, as shown in (Scheme 68).

Scheme 68



In order to obtain selenide **379**, we needed the α,β-unsaturated aldehyde **354**. This compound was made from saturated aldehyde **350** via selenide **382** (Scheme 69).

Scheme 69

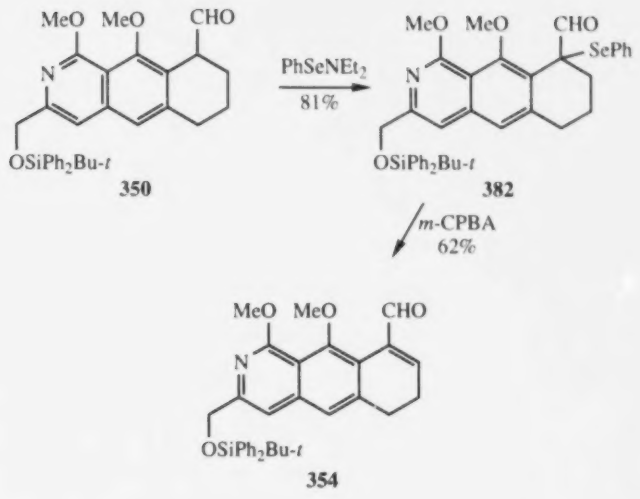


Table II Generation of unsaturated aldehyde **354**.

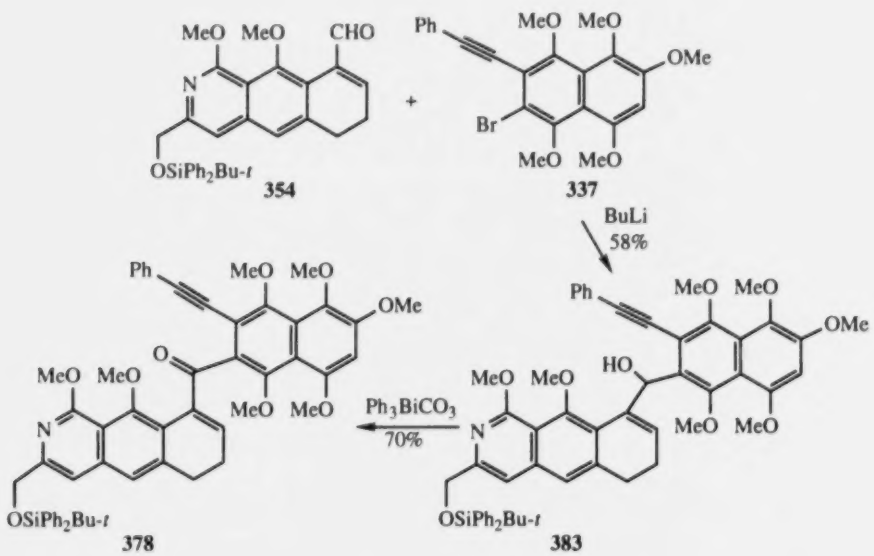
Entry	Conditions	Results	Desired Product
1	LDA, PhSeCl, -78 °C; then H_2O_2	Product and starting material (1:2)	Unsaturated aldehyde **354**
2	TMSOTf, Et_3N, 0 °C	Starting material	Silyl enol ether
3	LDA, PhSeCl, 0 °C; then H_2O_2	Product (20% yield)	Unsaturated aldehyde **354**
4	LDA, PhSeBr, HMPA 0 °C	Complex mixture	Selenide **382**
5	$PhSeNEt_2$; *m*-CPBA	Product (50% yield)	Unsaturated aldehyde **354**

Some difficulties were encountered in making aldehyde **354** (Table II). Standard conditions (LDA/PhSeCl, entry 1) gave a low yield of aldehyde **354**, after oxidation with hydrogen

peroxide. Using a higher temperature (entry 3) and a better leaving group (entry 4) did improve the yield. Attempts to make a silyl enol ether led only to recovered starting material (entry 2). We eventually found that the use of Reich's reagent, $PhSeNEt_2$[108] (entry 5), served to convert aldehyde **350** into the desired aldehyde **354** in moderate yield, after oxidation with *m*-CPBA.

Attempts to make γ-keto selenide **379.**

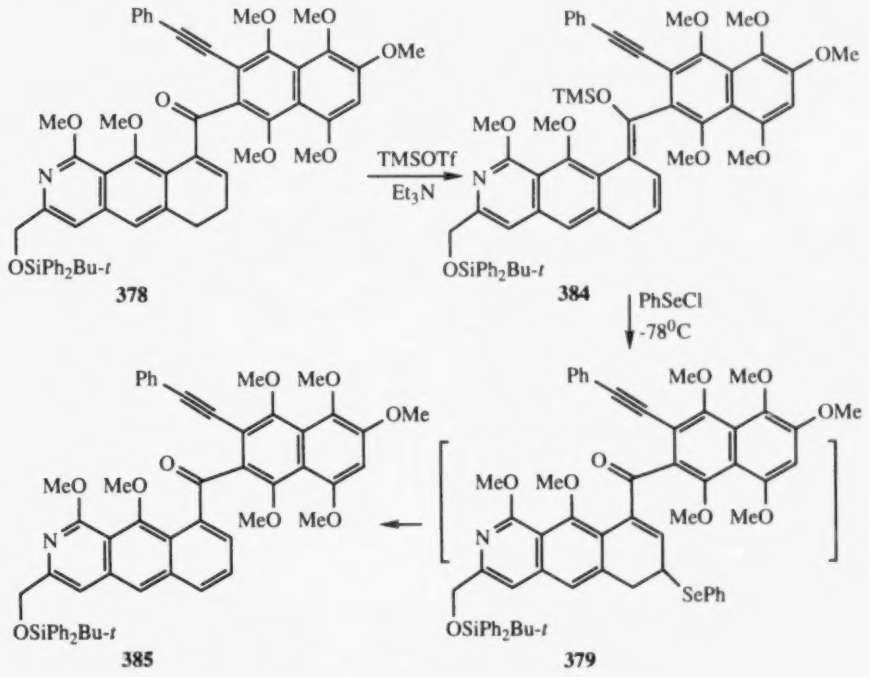
Scheme 70



Having generated the α,β-unsaturated aldehyde **354**, it was then coupled with bromide **337** to give alcohol **383** (Scheme 70). Oxidation with triphenylbismuth carbonate smoothly afforded the desired ketone **378**.

However, there was no selenation of ketone **378** under our standard conditions. In contrast to the saturated ketone **372**, the unsaturated analogue **378** can be transformed readily into its silyl enol ether **384** (whose stereochemistry was not established) (Scheme 71).

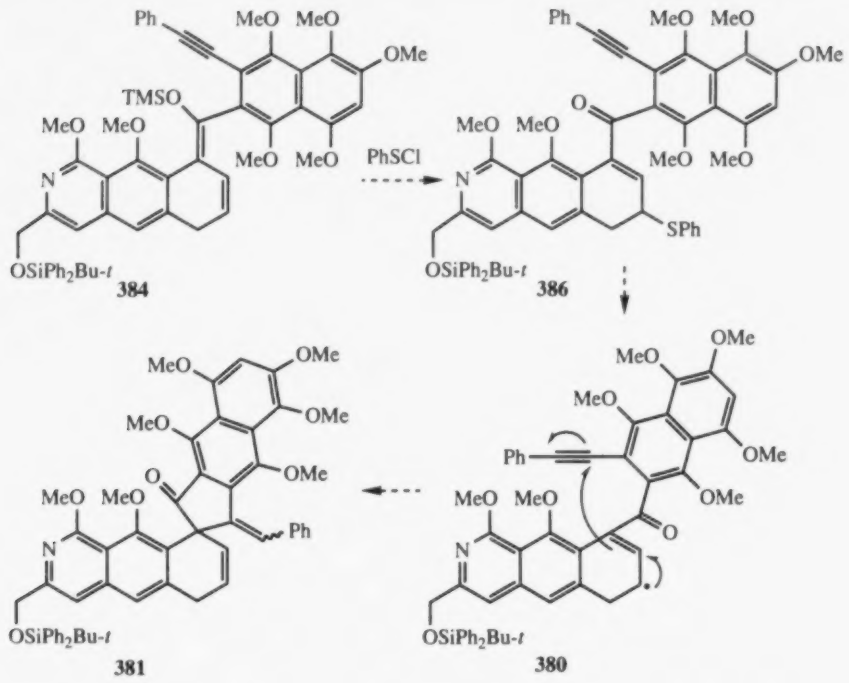
Scheme 71



Exposure of silyl enol ether **384** to phenylselenenyl chloride at a low temperature, surprisingly, gave aromatized product **385** (Scheme 71).

Since sulfides are well known to be more stable than selenides, we tried to introduce a phenylthio group into the silyl enol ether **384** (Scheme 72).

Scheme 72

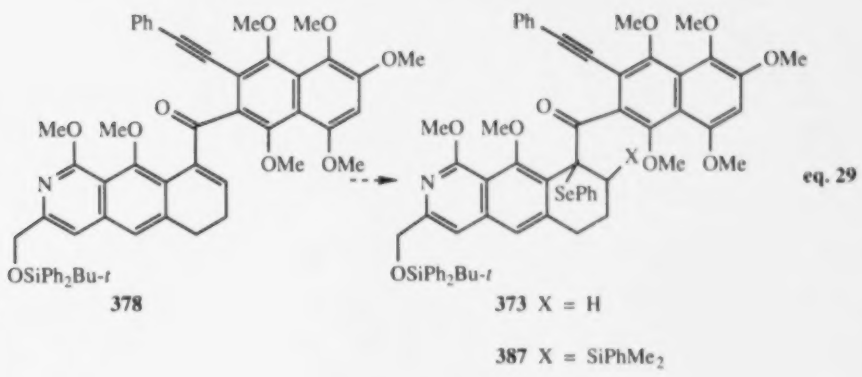


Unfortunately, treatment of silyl enol ether **384** with PhSCl, followed by triethylborane in the presence of triphenyltin hydride and air,[105] also resulted in the aromatized product **385**.

We now turned again to an α-ketoselenide. A conjugate addition-selenenylation sequence was tried in order to make α-ketoselenides **373** and **387** from the unsaturated ketone[111] **378** (eq. 29). However, only starting material or unidentified compounds were obtained.[a]

---

[a]TMSCl, CuH then PhSeCl (X = H) gave recovered starting material. L-Selectride, then PhSeCl (X = H) gave an unknown product. $LiSiPhMe_2$, CuCN then PhSeCl (X = $SiPhMe_2$) gave an unknown product.

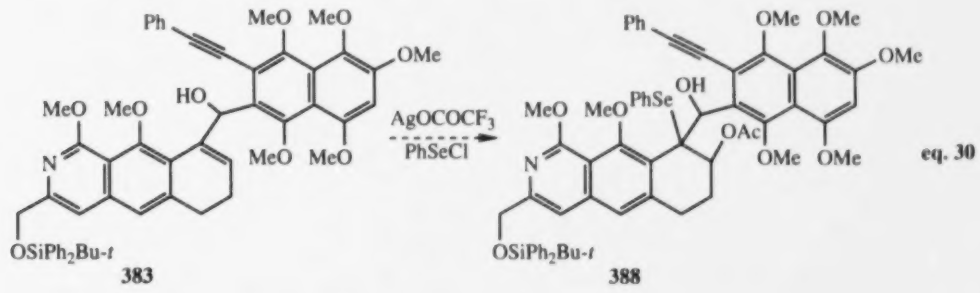


378 **373** X = H

387 X = $SiPhMe_2$

eq. 29

We also explored the possibility of making a β-hydroxy selenide from alcohol **383** (eq. 30).



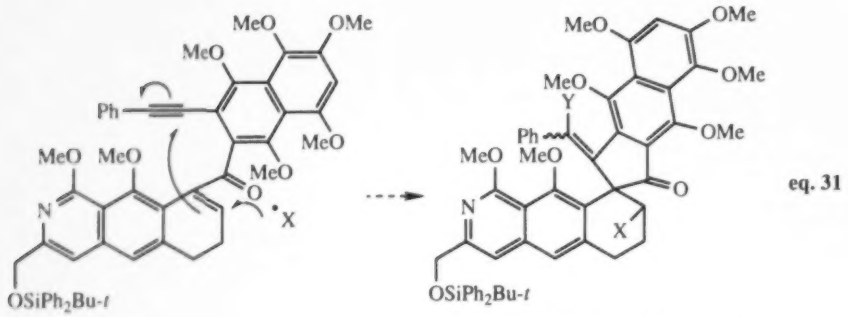
383 **388**

eq. 30

Addition of phenylselenenyl trifluoroacetate, generated *in situ* from phenylselenenyl chloride and silver trifluoroacetate, to alcohol **383** led to a complex mixture.

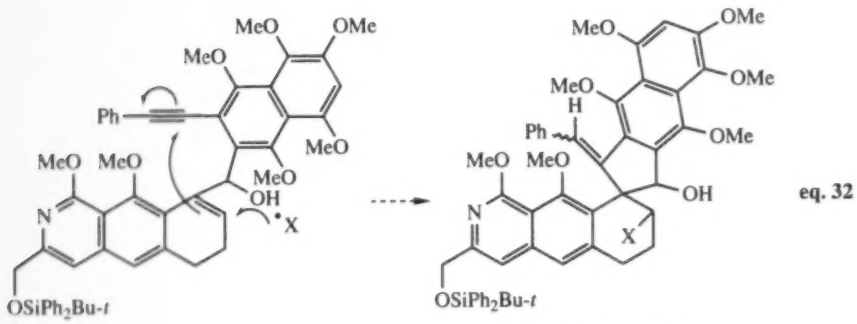
*Attempts at radical spirocyclization using olefins **383** and **378***

Since all efforts to make α- or γ-ketoselenides were fruitless, we wanted to see if the following radical



378 **389** X = SAc, Y = H; **390** X = Y = SPh; **391** X = SePh, Y = SPh

eq. 31



383 **392** X = Bu_3Sn; **393** X = AcS; **394** X = *t*-BuS

eq. 32

cyclizations would work (eq. 31 and eq. 32).[112] However, all our attempts at spirocyclizations with unsaturated alcohol **383**[a] or ketone **378**[b] were unsuccessful.

---

[a] Bu_3SnH, AIBN (desired reaction: **383→392**) gave a complex mixture. Bu_3SnH, Et_3B (desired reaction: **383→392**) gave recovered starting material. AIBN, AcSH (desired reaction: **383→393**) gave traces of **393**. $(PhCO)_2O_2$, AcSH (desired reaction: **383→393**) gave a complex mixture. $(PhCO)_2O_2$, *t*-BuSH (desired reaction: **383→394**) gave a complex mixture.

[b] AIBN, AcSH (desired reaction: **378→389**) gave 5% product. $PhCO)_2O_2$,

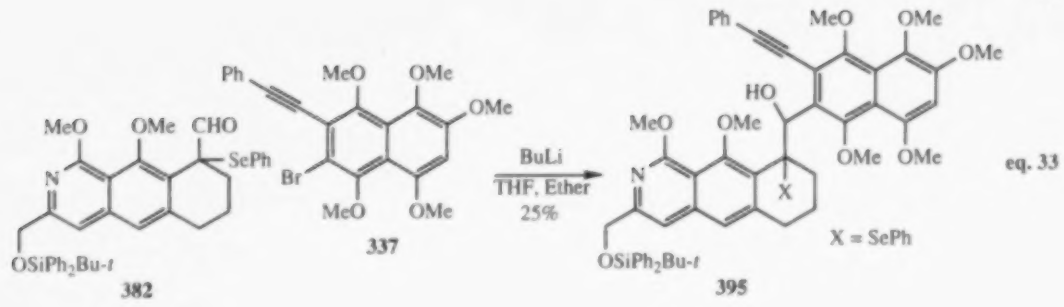
Spirocyclization of a β-hydroxy radical – an entry to the spiro[4,5]decane structure

As discussed above, the main problem was introduction of a PhSe group into a compound that would be properly constituted to undergo radical spirocylization. Since we could not introduce a PhSe group into ketone **372**, **378** or alcohol **383**, we tried to put the PhSe group onto the bottom piece aldehyde **350** *before coupling* with the top piece bromide (**337**).

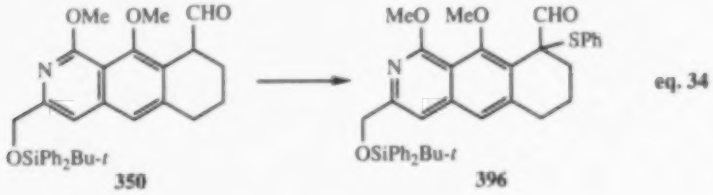
Synthesis of the third ABC subunit, the α-(phenylthio) aldehyde 396

Selenide **382** had been made in an earlier sequence (Scheme 69) and was found to be very unstable. Nonetheless, freshly made selenide **382** was coupled with bromide **337**. However, the yield was low (eq. 33), and, although the selenide **382** underwent desired radical cyclization (see later). We made some effort to prepare the more stable sulfide **396** (eq. 34).

AcSH (desired reaction: **378→389**) gave a complex mixture. $(PhS)_2$, hv [112c] (desired reaction: **378→390**) gave a complex mixture. $(PhS)_2$, $(PhSe)_2$ hv[112c] (desired reaction: **378→391**) gave a complex mixture.



Direct sulfenylation

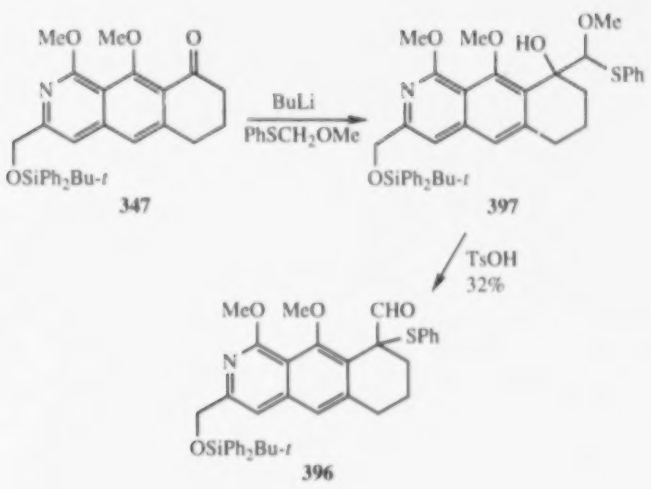


Deprotonation of aldehyde **350** with LDA, followed by addition of diphenyl disulfide in HMPA gave a low yield (30%) of sulfide **396**.[110] The use of potassium hydride and diphenyl disulfide[113] (0 °C) resulted in a complex mixture.

Rearrangement approach

A very interesting method of sulfenylation,[114] that we felt was applicable to our case, was examined next (Scheme 73).

Scheme 73



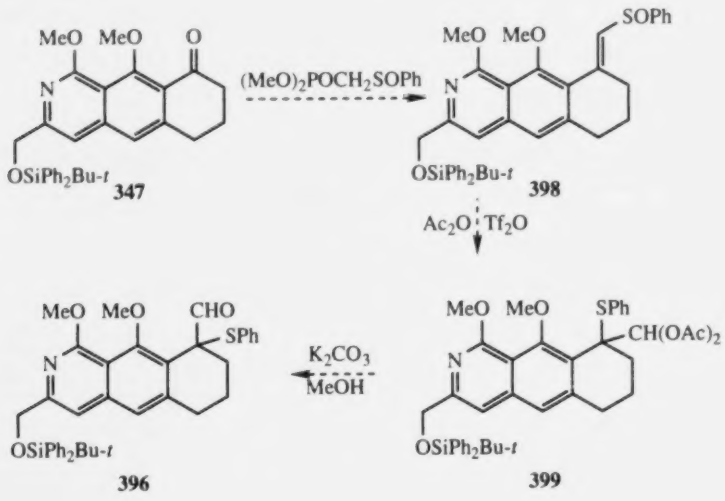
This process would lead to the desired sulfide **396** in two steps from ketone **347** (Scheme 73). However, there was no reaction under the literature conditions (1 equivalent $PhSCH_2OMe$,[115] BuLi, 30 min at -30 °C). We presume that the carbonyl group of ketone **347** is very unreactive as a result of conjugation to the two aromatic rings and two methoxy groups. Therefore, more vigorous conditions (5 equivalents $PhSCH_2OMe$, BuLi, 3 h -30 °C to room temperature) were used, and this time the desired alcohol **397** was produced. Rearrangement with toluenesulfonic acid in refluxing benzene then afforded the desired sulfide **396** in 32% overall yield.

Although this sequence works well on a small scale (less than 1 g), larger scale experiments often resulted in complex mixtures in the first step.

Vinyl Sulfoxide approach

Another approach we considered was the rearrangement of a vinyl sulfoxide (Scheme 74).[116]

Scheme 74

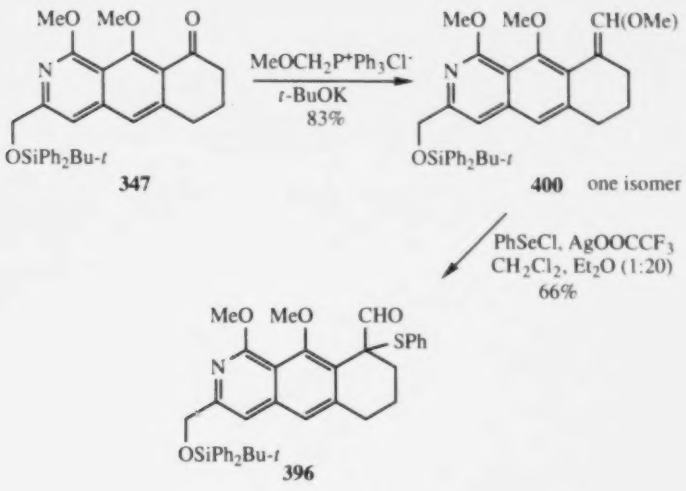


However, reaction of ketone **347** with $(MeO)_2POCH_2SOPh$ did not produce the desired sulfoxide **398**, and only starting material was recovered.

Enol ether approach

Nicolaou reported a method of converting enol ethers into selenides,[117] and this process was adapted to make sulfide **396** (Scheme 75).

Scheme 75



Enol ether **400** (stereochemistry not established) was readily made from ketone **347**, but it took a great deal of effort to convert this compound into phenylthio aldehyde **396** (Table III). Treatment of enol ether **400** with 2 equivalents of PhSCl in dichloromethane gave an aldehyde whose structure we were not able to deduce (even on the basis of extensive spectroscopic data) (entry 1). But, when 1 equivalent of PhSCl was used, a mixture of the desired aldehyde **396**, enol ether **400**, and the unknown aldehyde was obtained (entry 2). In order to improve the selectivity in favor of aldehyde **396**, a number of bases were added to the reaction mixtures, but without any success (entries 3, 4). We then switched our attention to changes in the solvent. When the reaction was run in more dilute dichloromethane, a 1:1 mixture of

Table III Conversion of enol ether **400** to phenylthio aldehyde **396.**

Entry	Conditions	Results
1	2 equiv. PhSCl, CH_2Cl_2, -78 °C	Unknown aldehyde
2	1 equiv. PhSCl, CH_2Cl_2, -78 °C	1:1:1 aldehyde **396**, starting material and unknown aldehyde
3	1 equiv. PhSCl, CH_2Cl_2, -78 °C, Et_3N	Starting material
4	1 equiv. PhSCl, CH_2Cl_2, -78 °C, pyridine	Traces of aldehyde **396**
5	1 equiv. PhSCl, ether, -78 °C then K_2CO_3	Traces of aldehyde **396**
6	1 eq PhSCl, ether, -78 °C	Aldehyde **396** major product
7	1.4 equiv. PhSCl, ether and CH_2Cl_2,	64% aldehyde **396** and 24% unknown aldehyde
8	1.3 equiv. PhSCl, ether and CH_2Cl_2	50% aldehyde **396**
9	1.3 equiv. PhSCl, ether and CH_2Cl_2, CF_3COOAg	66% aldehyde **396**

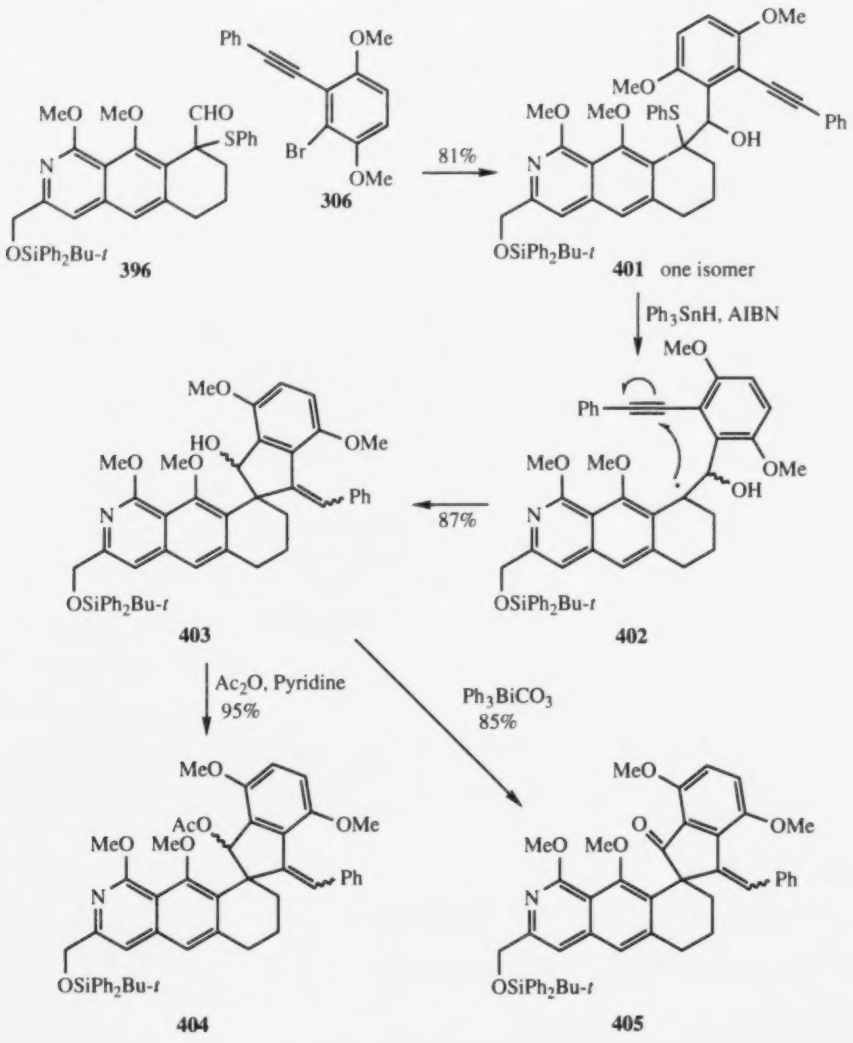
aldehyde **396** and starting material **400** (entry 5) was isolated, which we could not separate on silica gel, using a variety of solvents. In ether, only traces of product were generated after workup of the reaction mixture with potassium carbonate (entry 5), but the desired aldehyde **396** was isolated as the major product without workup (entry 6). Under optimized conditions (1.3 equivalents PhSCl, $AgOOCCF_3$, CH_2Cl_2/ether) aldehyde **396** was formed in 66% yield.

Radical spirocyclization - a model study

With phenylthio aldehyde **396** in hand, we were ready to generate a radical precursor which could undergo radical spirocylization. Since this approach is different from our previous work, we decided to examine a model system first.

Coupling of α-phenylthio aldehyde **396** with bromide **306** produced alcohol **401** (Scheme 76). This alcohol, containing a β-phenylthio group, was the desired precursor for radical spirocylization. In all our previous synthetic work on fredericamycin A,[35,79,81] we had dealt with α-keto radicals which were generated from selenides. However, in **401** we now have a potential β-hydroxy radical generated from a sulfide. Since the carbon-selenium bond is much weaker than the carbon-sulfur bond, and an α-keto radical is more stable than a β-hydroxyl radical, we expected that it would be more difficult to generate a radical from sulfide **401**. To our delight, under standard conditions, sulfide **401** underwent 5-*exo* radical closure to olefins **403** in 87% yield. In order to identify the product, we converted alcohols **403** into the acetates **404**. All data on alcohols **403** and acetates **404** showed that we had obtained the desired radical cyclization

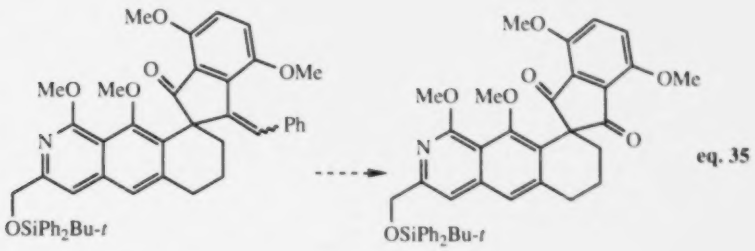
Scheme 76



product. Oxidation with triphenylbismuth carbonate then served to convert alcohols **403** into ketones **405**.

Cleavage of the exocyclic double bond in **405** proved to be an extremely difficult task. One-step double bond cleavage methods were considered first.

Attempted one step cleavage of the double bond



405 406

eq. 35

We tried to cleave the double bond of **405** directly (eq. 35). However, ozonolysis in dichloromethane or in methanol gave complex mixtures and other standard one-step cleavage methods (OsO_4, $NaIO_4$,[118] $KMnO_4$, $NaIO_4$[119]) also lead to complex mixtures. Therefore, dihydroxylation, followed by diol cleavage, was then explored (Scheme 77).

Attempted cis dihydroxylation and diol cleavage

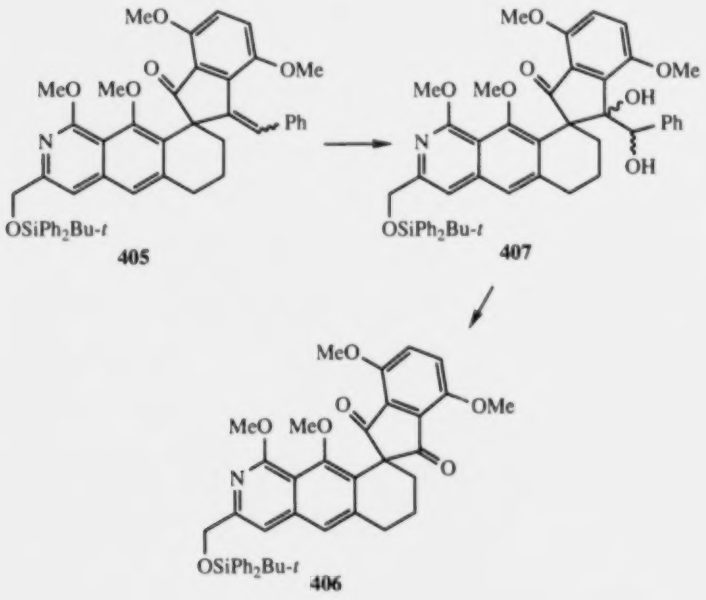
Vicinal dihydroxylation with osmium tetroxide was tried under a variety of conditions (using different solvents, different co-oxidants, and different workup methods).[a] Only

---

[a] OsO_4, pyridine gave recovered ketone **405** and an unknown compound. OsO_4, *t*-BuOH, pyridine gave recovered ketone **405** and an unknown compound. OsO_4, *t*-BuOH, *t*-BuOOH, Et_4NOH[121] gave recovered ketone **405**. OsO_4, pyridine (more concentrated than for the first attempt) gave 40% diol **407**. OsO_4, *t*-BuOH, NMO, pyridine gave recovered ketone **405**. OsO_4, $K_3Fe(CN)_6$ gave recovered ketone **405**. OsO_4, NMO, acetone[122] gave a complex mixture. OsO_4, ether[123] gave recovered ketone **405**. OsO_4, pyridine; $NaBH_4$ gave a complex mixture. I_2 and AgOAc[124] gave a complex mixture.

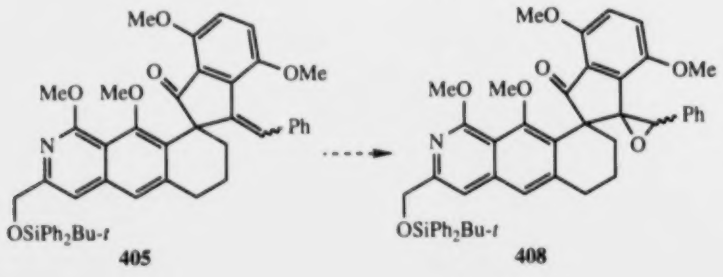
one procedure – use of concentrated pyridine solutions of osmium tetroxide – gave the desired product **407**, but in low yield. For a long time, we could not improve the yield, and so this approach was temporarily set aside.

Scheme 77



Epoxidation studies

Attempted epoxidation of ketone **405** under standard conditions[105] ($MeCN/H_2O_2$; *m*-CPBA/$NaHCO_3$; dimethyldioxirane) all led to complex mixtures (eq. 36).



eq. 36

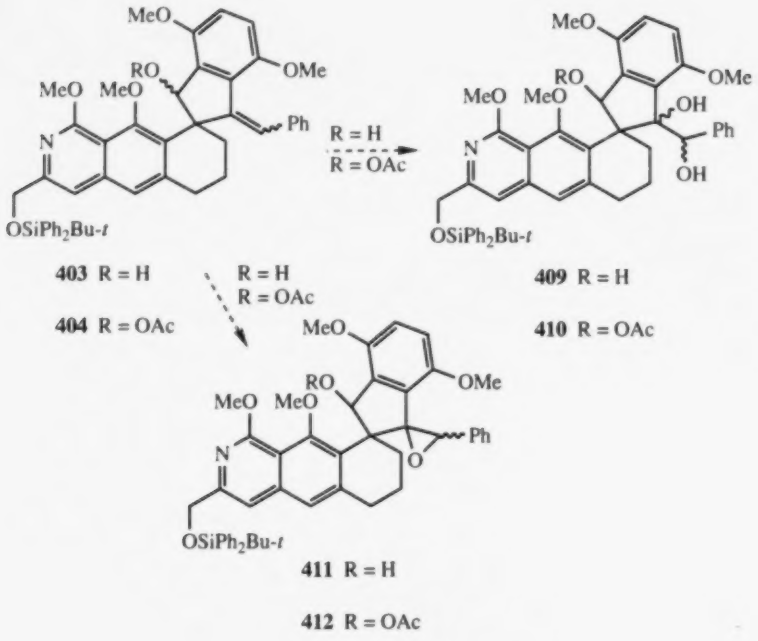
Attempts at double bond cleavage of alcohols ***403*** *and acetates* ***404***

Vicinal dihydroxylation of alcohols **403** with osmium tetroxide in pyridine afforded a low yield of ketones **405** along with some diol **407**, but there was no trace of triol **409** formed. Treatment of **403** with *m*-CPBA gave a complex mixture, and Sharpless epoxidation[125] [$V(acac)_2$, *t*-BuOOH] resulted in the formation of ketones **405** instead of the desired epoxide **411** (Scheme 77 and Scheme 78).

The above observations show that the hydroxyl group of **403** is easier to oxidize than the double bond, and so the alcohol was protected as the acetates **404** (see Scheme 76), and this material was examined next.

Treatment of acetates **404** with *m*-CPBA/$NaHCO_3$ did not lead to desired diol **410**, only a complex mixture was produced. Attempted dihydroxylation with osmium tetroxide in pyridine or in *tert*-butanol led only to recovery of **404** (Scheme 78).

Scheme 78



Finally, we returned to the dihydroxylation of ketones **405** and, eventually, after many experiments, we discovered some ways to improve this reaction:

1 Very concentrated osmium tetroxide solution should be used.

2 The reduction of the osmate ester is very slow; consequently, after adding sodium bisulfite, the mixture must be stirred for 20 min before product isolation.

Under optimum conditions, diketone **406** was obtained in 62% overall yield after diol cleavage with lead tetraacetate.

Elaboration of the side chain and completion of the synthesis of our first analog of fredericamycin A

With diketone **406** in hand, we were almost ready to attach the side chain. To prepare for this, the silicon protecting group was removed and the resulting alcohol was oxidized to an aldehyde (**414**) (Scheme 79), both steps being very efficient under standard conditions (tetrabutylammonium fluoride followed by manganese dioxide).

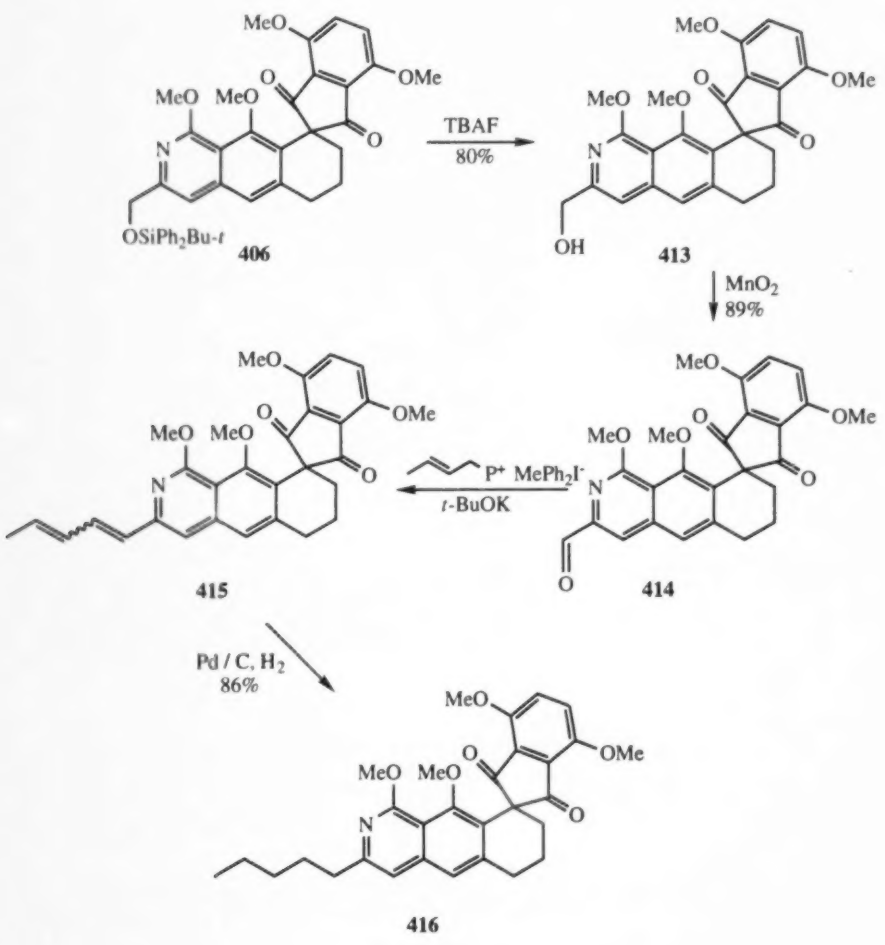
There were, however, some difficulties associated with construction of the side chain:

One problem was the poor solubility of aldehyde **414**; it hardly dissolves in ether, THF or dioxane. As a result, the rate of Wittig reaction was so low that only a low yield of product **415** was obtained. We were forced to use an unusual solvent (dichloromethane) for the Wittig reaction. To our delight, the reaction was finished in one minute in dichloromethane, and the yield was almost quantitative.

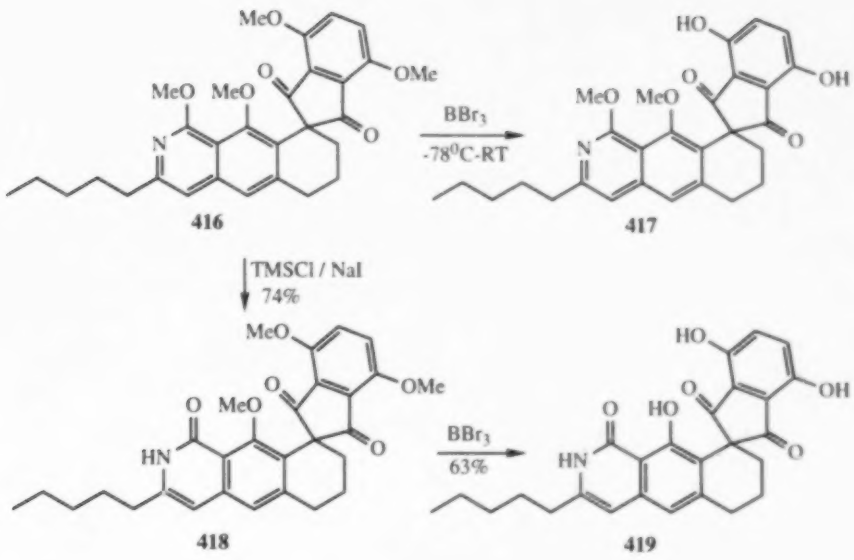
The other problem was that a mixture geometrical isomers was formed and these were inseparable by flash chromatography. Since this was only an analog, we decided to simplify the task by hydrogenation of the double bonds to produce **416** (Scheme 79). Deprotection of **416** with BBr_3 removed[78] only two of the four *O*-methyl groups (**416**→**417**), and complete demethylation has to be done in two steps (Scheme 80): treatment of **416** with trimethylsilyl chloride and sodium iodide afforded **418**; then exposure of **418** to boron tribromide served to take off the remaining three *O*-

methyl groups. Thus, the synthesis of our first analog of fredericamycin was completed.

Scheme 79



Scheme 80



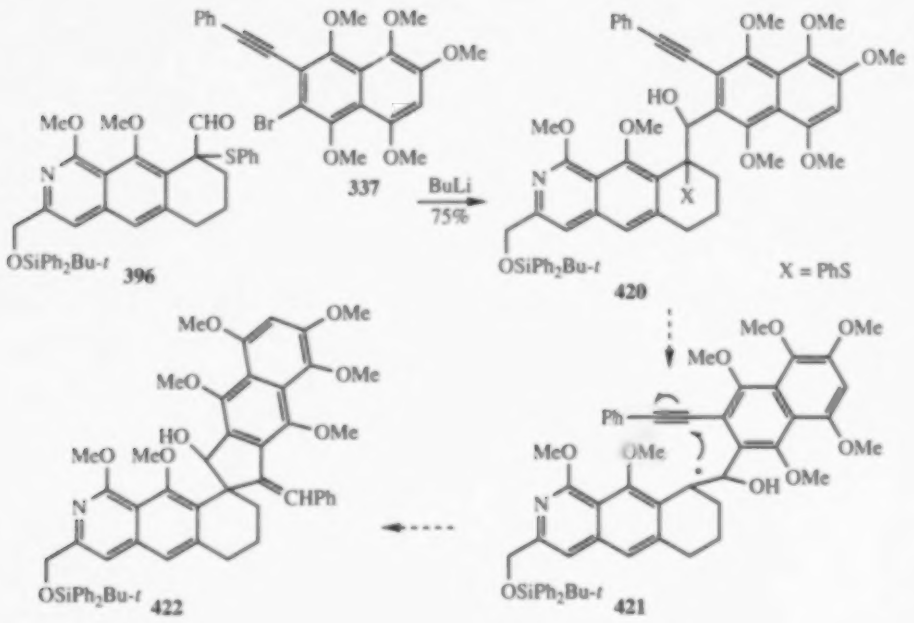
Synthesis of tetrahydrohomofredericamycin A

As discussed above, the radical generated from a β-hydroxyl sulfide cyclizes in a way that allowed us to prepare our first analogue of fredericamycin A. With this approach in hand, we were ready to make our more sophisticated target, tetrahydrohomofredericamycin A (**335**).

Radical spirocyclization

Coupling of aldehyde **396** with bromide **337** gave rise to alcohol **420** as a single isomer, which was the desired radical precursor. However, our standard radical cyclization conditions (triphenyltin hydride and AIBN in refluxing benzene or triethylborane and triphenyltin hydride in hexane[82]) gave either a complex mixture or recovered starting material, instead of proceeding via **421** to **422** (Scheme 81).

Scheme 81

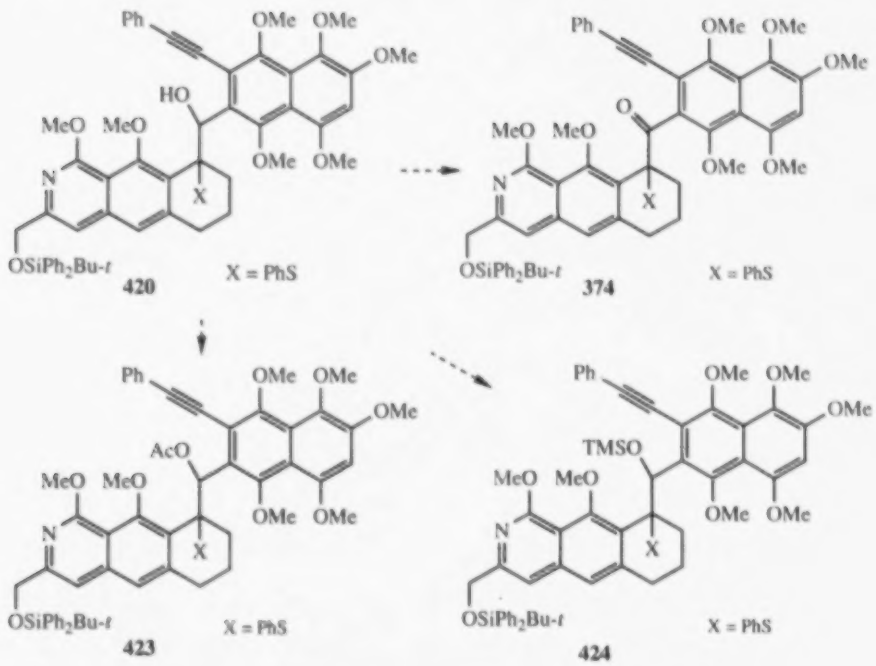


It is well known, especially from work done in this laboratory,[78] that α-keto radicals are very easy to generate. Therefore, we tried to convert alcohol **420** into ketone **374** (Scheme 82). However, under a number of oxidation conditions (DDQ, Swern, triphenylbismuth carbonate, manganese dioxide) only complex mixtures or unidentifiable compounds were formed.

We then decided to protect alcohol **420** and see if the protected alcohol would undergo radical cyclization. Surprisingly, all attempts to protect alcohol **420** (Ac_2O, 4-dimethylaminopyridine) as an acetate (**423**) or silyl ether (**424**) (trimethylsilyl chloride, triethylamine) were unsuccessful and from each experiment we recovered the

starting alcohol.

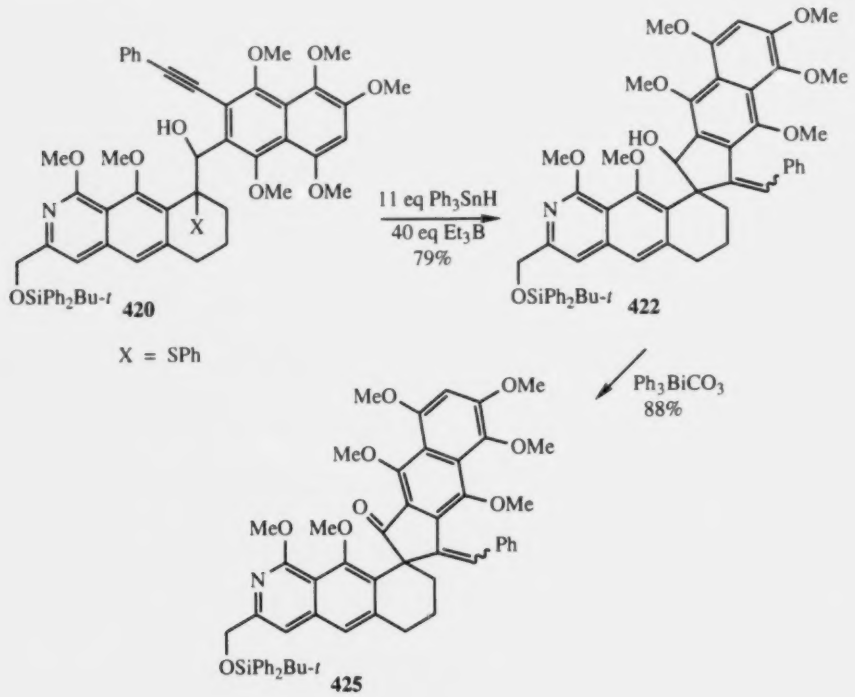
Scheme 82



We were forced, therefore, to reexamine alcohol **420**. When the attempted radical cyclization with triethylborane was repeated, a trace amount of a new compound was noticed. If this was the desired product, we might be able to get it in good yield by use of *concentrated triethylborane* solutions. Indeed, treatment of alcohol **420** with an excess of triethylborane (40 equiv.) and triphenyltin hydride (11 equiv.), in the presence of air, gave the desired radical cyclization product **422** (as a mixture of isomers) in 79% yield (Scheme 83). We had made earlier selenide **395**,

corresponding to **420**. The selenide can also cyclized to give the desired product **422** (50% yield) under the same conditions. Oxidation with triphenylbismuth carbonate then afforded ketones **425** whose stereochemistry was not known. With this material in hand, we were ready to cleave the exocyclic double bond.

Scheme 83

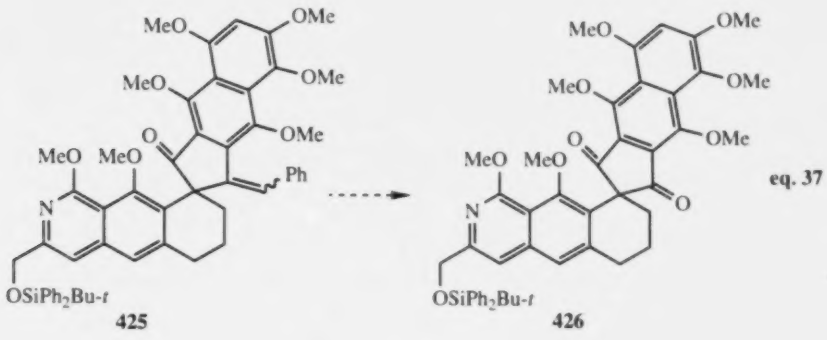


Cleavage of the carbon-carbon double bond

Even with the double bond cleavage experience we had gained with model compound **405**, it was still extremely difficult to cleave the exocyclic double bond in **425**. As usual, we tried the simplest methods first.

Attempted one step cleavage of the double bond

Several methods of double bond cleavage[126] (*cf.* eq. 37) led to complex mixtures or recovered **425**.[a]



eq. 37

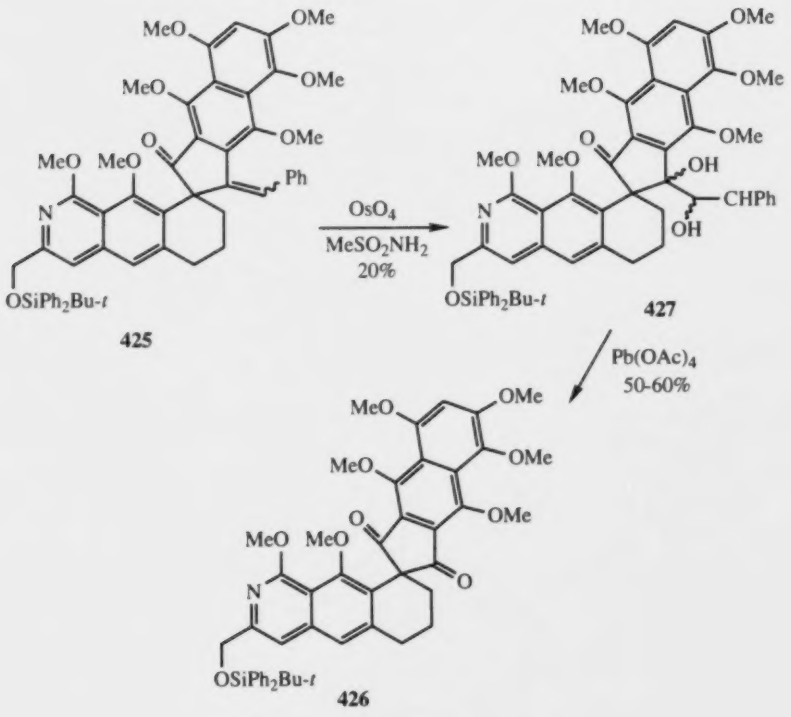
Dihydroxylation-diol cleavage

Vicinal dihydroxylation with concentrated osmium tetroxide in pyridine at room temperature gave only a low yield (13%) of diols **427**, and use of higher temperatures (50 °C) did not improve the yield. Addition of methanesulfonamide[127] gave 20% of diol **427**, which was converted into diketone **426** by the action of $Pb(OAc)_4$ (Scheme 84). All other attempts to raise the yield of **427** were unsuccessful.

---

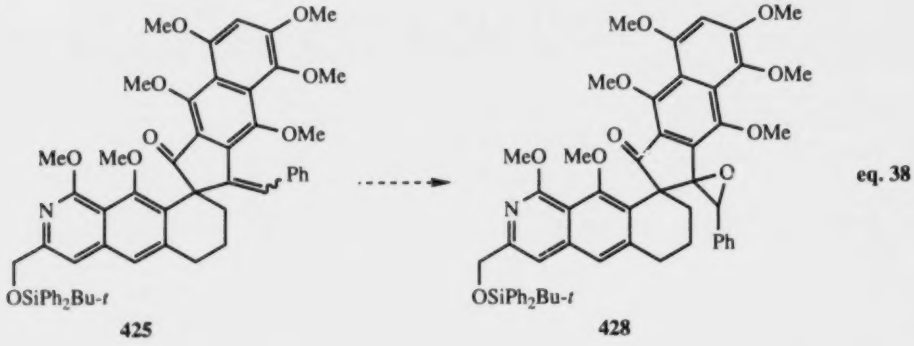
[a]Complex mixtures were obtained with: O_3, pyridine and CH_2Cl_2; RuO_2 and $NaIO_4$; $RuCl_3$ and $NaIO_4$; OsO_4, HIO_4, and pyridine; O_2, hν. RuO_2, O_2, and CH_3CHO gave recovered starting material.

Scheme 84



Attempted epoxidation

Standard epoxidation conditions (*m*-CPBA, H_2O_2/MeCN) gave either complex mixtures or recovered ketone **425** (*cf.* eq. 38).

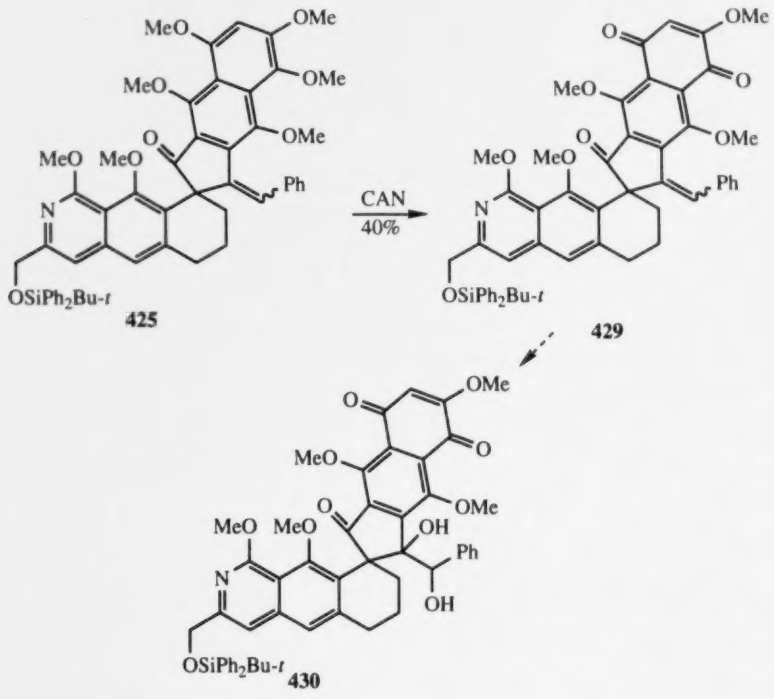


eq. 38

When a strong epoxidation agent (dimethyldioxirane) was used, an unidentified compound in which the double bond was still present was isolated.

Attempted dihydroxylation on modified ketones

Scheme 85

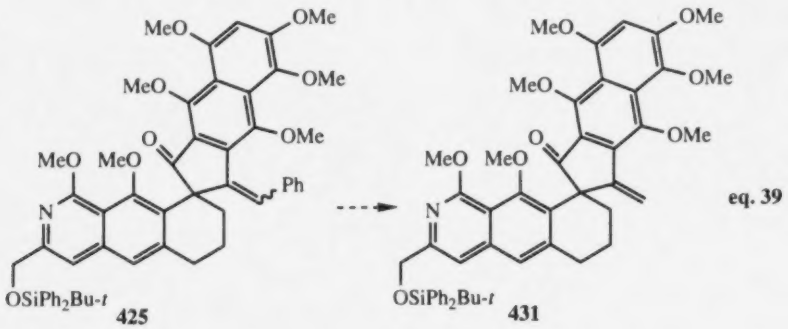


Since dihydroxylation of ketones **425** gave a low yield of diols **427**, we tried to modify ketone **425** in a way that would facilitate diol formation.

Oxidative demethylation with ceric ammonium nitrate generated quinone **429** (Scheme 85), which was treated with osmium tetroxide in pyridine, but **429** was recovered, and none

of the diol **430** was formed.

As disubstituted double bonds are easier to cleave than trisubstituted double bonds, we examined the possibility of the following transformation (eq. 39):

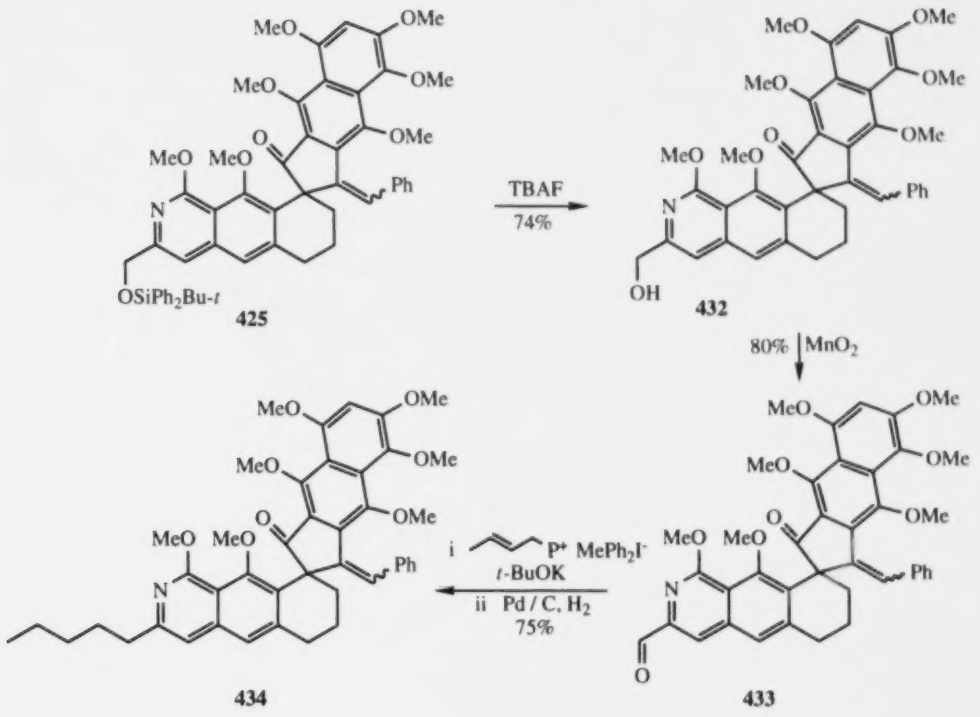


Exposure of ketone **425** to 1 equivalent of Tebbe's reagent and 4-dimethylaminopyridine led to recovery of starting material.[128] When an excess of Tebbe's reagent was used, a complex mixture was formed.

Another possibility was to build up the side chain before cleavage of the double bond. This approach appeared to be attractive because we would be only two steps from the end if this method worked.

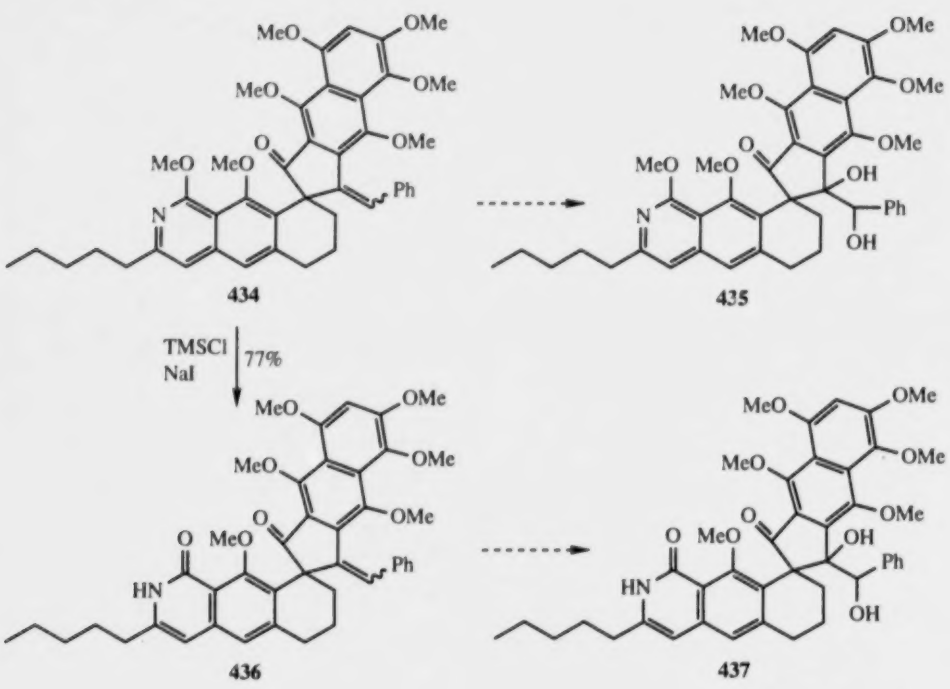
Desilylation under standard conditions (Scheme 86) afforded alcohol **432**, which was oxidized into aldehyde **433**. Wittig chain extension, followed by hydrogenation gave the desired olefin **434**. However, there was no reaction of olefin **434** with osmium tetroxide in pyridine at room temperature.

Scheme 86



When the reaction was run at 50 °C, a complex mixture was formed. Olefin **434** was further transformed into **436** (Scheme 87), which was treated with osmium tetroxide in pyridine; again only a complex mixture was formed.

Scheme 87

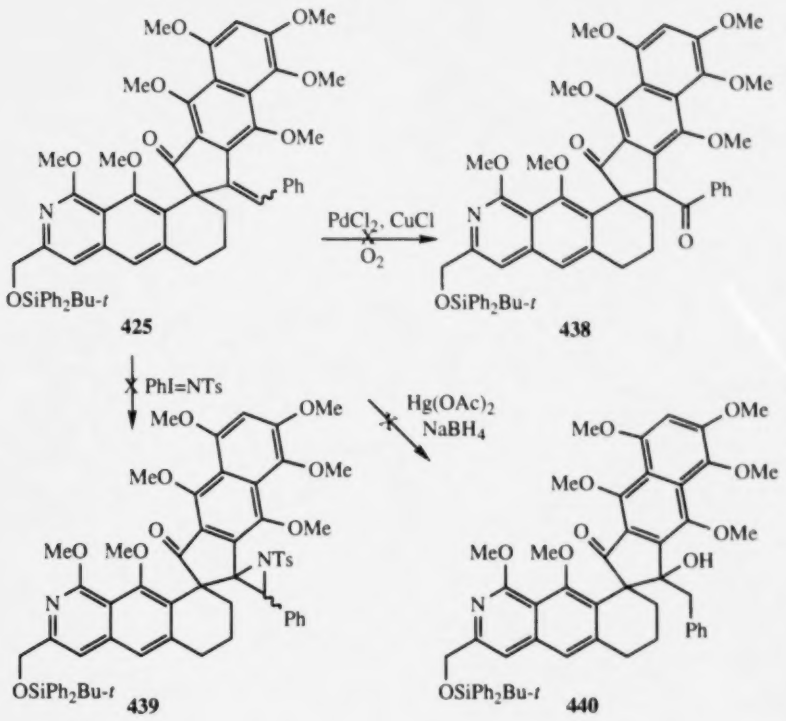


Other reactions on the double bond

We made a few other attempts to solve the problem of cleaving the exocyclic double bond in good yield.

To our surprise, oxymercuration and palladium catalyzed oxidation[129] all gave back olefin **425** (Scheme 88). Copper-catalyzed aziridination[130] afforded a mixture of two compounds in which the exocyclic double bond was still present.

Scheme 88



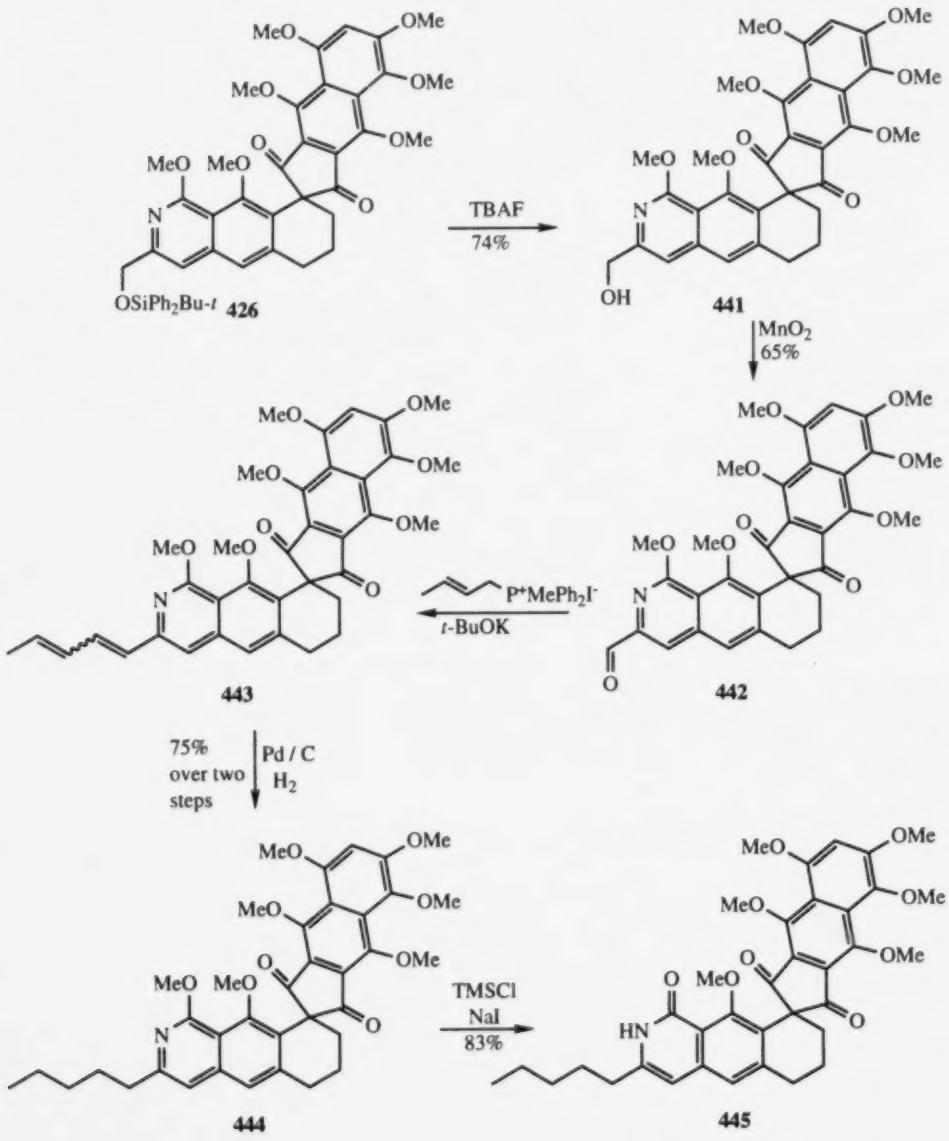
From the above experiments, it is evident that the trisubstituted and fully conjugated (to the aromatic rings) exocyclic double bond in olefin **425** is very unreactive. Examination of space-filling models also shows that the bond is more sterically hindered than in the corresponding compound leading to fredericamycin A itself. In addition, the aromatic ring system is electron rich due to the methoxy groups; consequently, the aromatic rings rather than the double bond can easily be the preferred site of oxidation.

We concluded that we would have to accept the low yield (20%) in the dihydroxylation, and we proceeded to complete the synthesis with the material we had in hand.

Completion of the synthesis of tetrahydrohomo-fredericamycin A

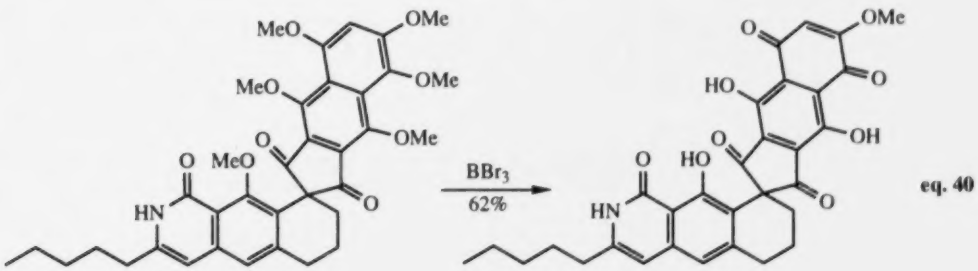
Attaching the side chain to diketone **426** was

Scheme 89



straightforward. Desilylation with TBAF (Scheme 89), followed by oxidation, gave aldehyde **442**. Wittig reaction then afforded alkene **443** as a mixture of isomers, which was hydrogenated to **444**. The *O*-methyl group on A ring was then removed with trimethylsilyl iodide, generated *in situ* from trimethylsilyl chloride and sodium iodide.

Removal of the remaining five *O*-methyl groups posed some problem, and for a long time, we could not get a pure product (**335**). All efforts to purify the crude product by flash chromatography in different solvents systems or by recrystallization were unsuccessful. Eventually, it was discovered that the starting material **445** is not stable and will decompose within 24 hours, even in freezer. The impurities were introduced by impure starting material. When freshly purified **445** was used, a pure (^{1}H NMR, 400 MHz) product (**335**) was easily isolated (eq. 40).

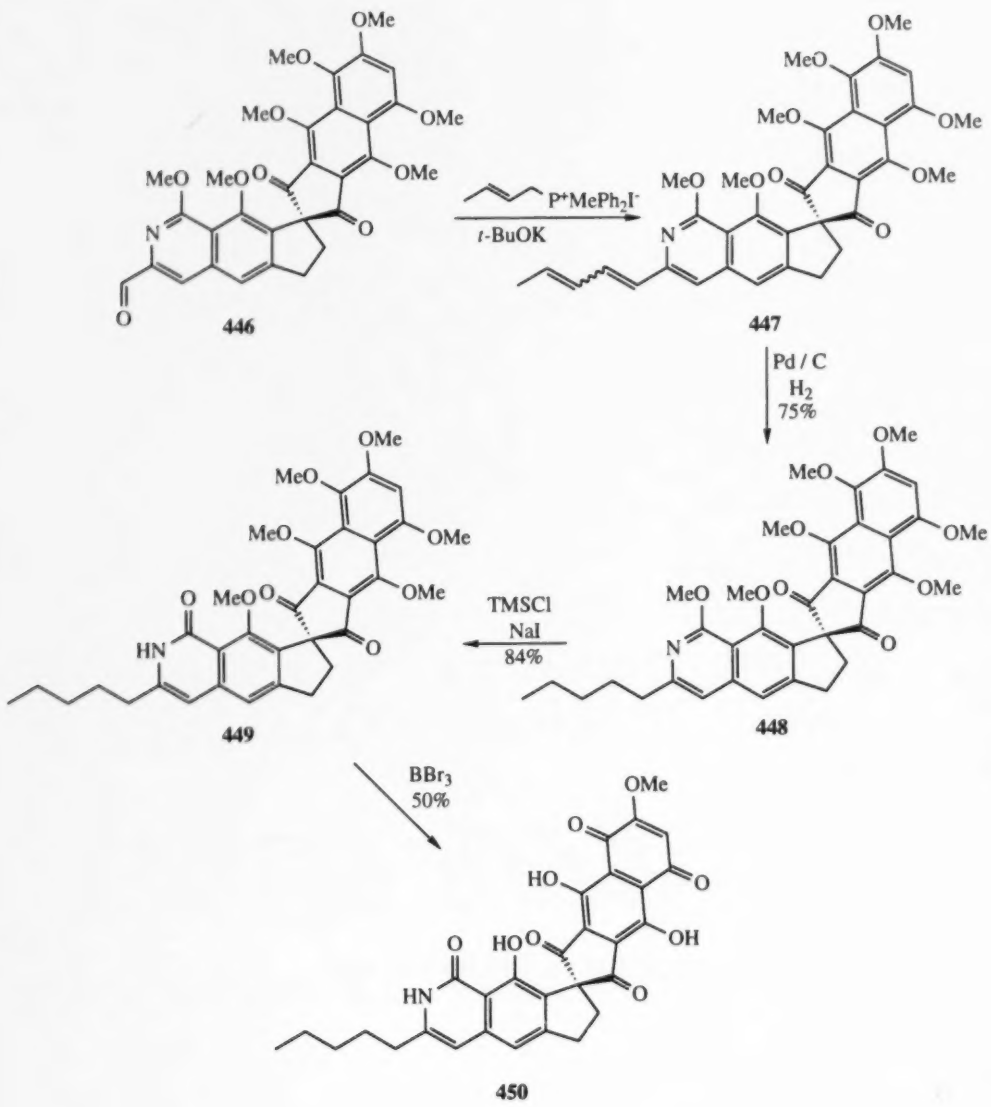


445 335 eq. 40

For the convenience of comparison, tetrahydrofredericamycin A was also made similarly, using aldehyde **446** which is a intermediate in the synthesis of

fredericamycin A (Scheme 90).

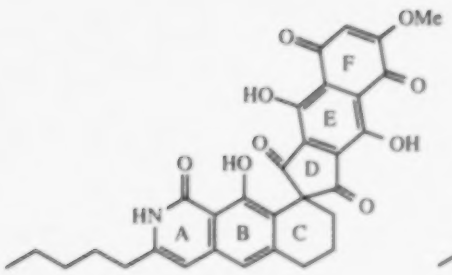
Scheme 90



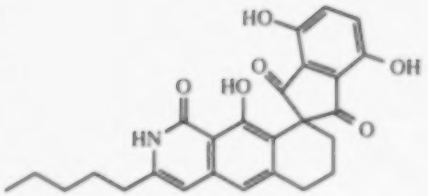
Conclusions

The total synthesis of tetrahydrohomofredericamycin A (**335**), an analog of the natural product fredericamycin A, in

which the C-ring has been expanded from a five-membered ring to a six-membered ring, and the side chain has been saturated, was completed. The simpler analogue **419** was also prepared. Due to the sensitivity of ring C to aromatization, our approach had to be different from that used in the synthesis of the natural product fredericamycin A itself. Also, the exocyclic double bond of the intermediate **425** was much more difficult to cleave - probably for steric reasons - than the corresponding bond in the series leading to fredericamycin A. However, enough of **335** was synthesized to allow biological testing that would evaluate the influence of the changes we had made to the structure of the natural product. The two compounds have been submitted to the NIH for evaluation, but the results are not available yet. The six-membered C-ring confers additional conformational mobility on the spiro system, compared with fredericamycin A itself, and also alters the angle between the two flat component parts of the substance. It is of interest to establish if these changes are reflected in a change in biological activity, especially as the spirodiketone system of fredericamycin A represents a unique feature among antitumor agents. It should be noted that the absolute configuration of fredericamycin is not known, and that our material is racemic. If sufficiently high biological activity is found for our compounds it would then be worthwhile to attempt the synthesis of optically pure material.



335



419

An efficient radical cyclization for the construction of the spiro[4,5]decane structures of **335** and **419** was developed in our work. This methodology is especially useful for the synthesis of sterically congested spiro compounds. It is unusual in that the relatively unreactive alkyl sulfide unit was used as the radical precursor. In our approach to spiro systems, the top piece organolithium was added to an α-phenylthio aldehyde so that, unlike the case of the synthesis of fredericamycin A, the radical precursor was introduced *before* the top and bottom units were joined.

III Experimental Section

General Procedures. Unless stated to the contrary, the following conditions apply. Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[131] and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography and extractions were distilled before use.

Products were isolated from solution by evaporation under water-aspirator vacuum at, or below, room temperature, using a rotary evaporator.

All the compounds purified by chromatography were pure as judged by TLC analysis.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Melting points were determined on a Kofler block melting

point apparatus.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid,[132] followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF and Et_2O were distilled from Na and benzophenone ketyl. Dry PhH was distilled from sodium. Dry Et_3N, CH_2Cl_2, MeOH, MeCN, and pyridine were distilled from CaH_2. Commercial (Aldrich) solutions of *n*-BuLi and MeLi were assumed to have the stated molarity. Petroleum ether refers to the fraction boiling at 60-90 °C.

FTIR measurements were made as casts from the specified solvent using potassium bromide plates.

The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS9 (modified), or Kratos MS50 (modified) mass spectrometers.

Microanalyses were performed by the Microanalytical Laboratory of this Department.

α-Cyclopentyl[3,6-dimethoxy-2-(phenylethynyl)phenyl]-methanol (307).

306 **307**

n-BuLi (1.5 M in hexanes, 0.53 mL, 0.79 mmol) was injected dropwise into a stirred and cooled (-78 °C) solution of bromide **306** (264 mg, 0.78 mmol) in Et_2O (6 mL). The mixture was stirred for an additional 30 min, and cyclopentanecarboxaldehyde[83] (77.1 mg, 0.78 mmol) in Et_2O (3 mL plus 1 mL as a rinse) was then added over *ca*. 3 min. The cold bath was left in place for 2 h, by which time the temperature had risen to 0 °C. Saturated aqueous NH_4Cl (10 mL) was added, and the mixture was extracted with Et_2O (2 x 25 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm), using 7:13 EtOAc-hexane, gave alcohol **307** (228.4 mg, 82%) as a homogeneous (^1H NMR, 300 MHz), white solid: mp 123.0-123.5 °C; FTIR (neat) 3560, 2953, 1590, 1477 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21--1.76 (m, 7 H), 1.88--1.98 (m, 1 H), 2.48--2.62 (m, 1 H), 3.69 (d, *J* = 11.4 Hz, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 5.04 (dd, *J* = 9.2, 9.2 Hz, 1 H), 6.75 (d, *J* = 8.8 Hz, 1 H), 6.86 (d, *J* = 8.8 Hz, 1 H), 7.32--7.39 (m, 3 H),

7.50--7.56 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.40 (t'), 25.51 (t'), 29.13 (t'), 30.48 (t'), 46.49 (d'), 55.91 (q'), 56.47 (q'), 76.56 (d'), 84.11 (s'), 98.7 3 (s'), 109.52 (d'), 111.97 (d'), 112.64 (s'), 123.47 (s'), 128.37 (d'), 131.52 (d'), 135.21 (s'), 151.40 (s'), 154.73 (s') (two signals overlap); exact mass *m/z* calcd for $C_{22}H_{24}O_3$ 336.1725, found 336.1721. Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.51; H, 7.26.

[Cyclopentyl][3,6-dimethoxy-2-(phenylethynyl)phenyl]-methanone (308).

307 **308**

Alcohol **307** (1.28 g, 3.79 mmol) in CH_2Cl_2 (25 mL) was added at room temperature to a stirred mixture of pyridinium chlorochromate (3.30 g, 15.2 mmol) and 3Å molecular sieves (8.0 g) in CH_2Cl_2 (62.0 mL). Stirring was continued for 6 h, Et_2O (100 mL) was then added, and the suspension was filtered through a pad (5 x 6 cm) of Celite, which was washed well with 1:1 Et_2O-CH_2Cl_2. The combined filtrates were evaporated, and flash chromatography of the residue over silica gel (6 x 15 cm), using 3:7 EtOAc-hexane, gave ketone **308** (1.08 g, 85%) as a homogeneous (^1H NMR, 300 MHz) solid: mp 88.5-89.3 °C;

FTIR (neat) 1700, 1575 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.51--1.90 (m, 6 H), 1.99--2.12 (m, 2 H), 3.44--3.55 (m, 1 H), 3.79 (s, 3 H), 3.90 (s, 3 H), 6.85 (d, J = 9.0 Hz, 1 H), 6.89 (d, J = 9.0 Hz, 1 H), 7.31--7.38 (m, 3 H), 7.48--7.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 26.30 (t'), 29.04 (t'), 52.95 (d'), 56.71 (q'), 56.95 (q'), 83.57 (s'), 97.84 (s'), 110.62 (s'), 112.10 (d'), 112.82 (d'), 123.44 (s'), 128.56 (d'), 128.74 (d'), 131.95 (d'), 136.31 (s'), 149.71 (s'), 154.66 (s'), 207.96 (s'); exact mass m/z calcd for $C_{22}H_{22}O_3$ 334.1569, found 334.1571. Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.02; H, 6.63. Found: C, 78.86; H, 6.60.

[Cyclopentylidene[3,6-dimethoxy-2-(phenylethynyl)-phenyl]methoxy]trimethylsilane (309).

308 **309**

TMSOTf (1.79 g, 5.34 mmol) was injected into a stirred and cooled (ice bath) mixture of ketone **308** (1.79 g, 5.34 mmol) and Et_3N (11.45 mL, 82.15 mmol) in dry CH_2Cl_2 (182 mL). The mixture was stirred for 1 h. Saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over

silica gel (5 x 15 cm), using 1:4 EtOAc-hexane, gave silyl enol ether **309** (2.00 g, 92%) as a homogeneous (^{1}H NMR, 300 MHz), white solid: mp 87.0-88.0 °C; FTIR (CH_2Cl_2 cast) 1320, 1177, 1167, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.01 (s, 9 H), 1.49--1.80 (m, 4 H), 1.84--1.98 (m, 1 H), 2.28--2.52 (m, 2 H), 2.52--2.67 (m, 1 H), 3.81 (s, 3 H), 3.89 (s, 3 H), 6.81 (d, *J* = 9.6 Hz, 1 H), 6.85 (d, *J* = 9.6 Hz, 1 H), 7.28--7.38 (m, 3 H), 7.45--7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 0.00 (q'), 25.88 (t'), 26.61 (t'), 28.57 (t'), 29.04 (t'), 55.65 (q'), 55.84 (q'), 85.01 (s'), 95.73 (s'), 109.89 (d'), 111.49 (d'), 113.29 (s'), 123.40 (s'), 126.28 (s'), 127.33 (d'), 127.62 (d'), 130.94 (d'), 131.60 (s'), 135.08 (s'), 151.31 (s'), 153.62 (s'); exact mass *m/z* calcd for $C_{25}H_{30}O_3Si$ 406.1964, found 406.1979. Anal. Calcd for $C_{25}H_{30}O_3Si$: C, 73.85; H, 7.44. Found: C, 74.09, H, 7.57.

[1-(Phenylseleno)cyclopentyl][3,6-dimethoxy-2-(phenylethynyl)phenyl]methanone (310).

309 **310**

PhSeCl (1.00 g, 5.2 mmol) in THF (4 mL plus 1 mL as a rinse) was added to a stirred and cooled (-78 °C) solution of silyl enol ether **309** (1.42 g, 3.50 mmol) in THF (60 mL).

Stirring was continued for 2 h, and the mixture was then diluted with EtOAc (500 mL) and washed with saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 1:3 EtOAc-hexane, gave selenide **310** (1.56 g, 91%) as a homogeneous (^1H NMR, 300 MHz), yellow oil: FTIR (CH_2Cl_2 cast) 1682, 1476, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.68--1.78 (m, 2 H), 1.80--1.98 (m, 4 H), 2.20--2.38 (m, 2 H), 3.71 (s, 3 H), 3.88 (s, 3 H), 6.85 (s, 2 H), 7.25--7.45 (m, 8 H), 7.63--7.68 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 24.57 (t'), 36.62 (t'), 55.93 (q'), 56.67 (q'), 65.39 (s'), 83.93 (s'), 97.79 (s'), 111.01 (s'), 111.73 (d'), 112.42 (d'), 123.09 (s'), 128.19 (d'), 128.40 (d'), 128.54 (d'), 128.69 (d'), 129.45 (s'), 131.67 (d'), 134.54 (s'), 137.54 (d'), 149.36 (s'), 154.54 (s'), 204.92 (s'); exact mass *m/z* calcd for $C_{28}H_{26}O_3Se$ 490.1047, found 490.1049.

(*Z*)-4,7-Dimethoxy-3-(phenylmethylene)spiro[2*H*-indene-2,1'-cyclopentan]-1(3*H*)-one (312).

310 **312**

AIBN (10.0 mg, 0.061 mmol) was tipped into a solution of

selenide **310** (336 mg, 0.69 mmol) in dry PhH (10.0 mL) under Ar. The mixture was lowered into an oil bath set at 80 °C and, as soon as the solution began to reflux, Ph_3SnH (0.26 mL, 1.02 mmol) in dry PhH (3 mL plus 0.5 mL as a rinse) was added over *ca.* 2 min. Refluxing was continued for 20 min and the solvent was then evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using increasing amounts of EtOAc in hexane (from 1:3 to 2:3), gave spiroketone **312** (217 mg, 95%) as a homogeneous (^1H NMR, 300 MHz) solid: mp 172.5-174.0 °C; FTIR (CH_2Cl_2 cast) 1708, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24--1.42 (m, 2 H), 1.65--2.05 (m, 6 H), 3.92 (s, 3 H), 3.93 (s, 3 H), 6.81 (d, *J* = 12 Hz, 1 H), 7.11 (d, *J* = 12 Hz, 1 H), 7.23--7.40 (m, 5 H), 8.06 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 26.97 (t'), 37.12 (t'), 55.83 (q'), 56.04 (q'), 58.91 (s'), 110.76 (d'), 117.86 (d'), 122.98 (s'), 126.76 (d'), 128.02 (d'), 128.92 (d'), 129.00 (d'), 137.96 (s'), 138.89 (s'), 143.55 (s'), 150.80 (s'), 151.92 (s'), 208.13 (s'); exact mass *m/z* calcd for $C_{22}H_{22}O_3$ 334.1569, found 334.1568. Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.02; H, 6.63. Found: C, 78.66; H, 6.66. Irradiation of the methoxy signal at δ 3.93 in the ^1H NMR spectrum caused a nuclear Overhauser enhancement of 9% in the vinyl hydrogen signal, at δ 8.06.

4,7-Dimethoxyspiro[2*H*-indene-2,1'-cyclopentane]-1,3-dione (313).

312 313

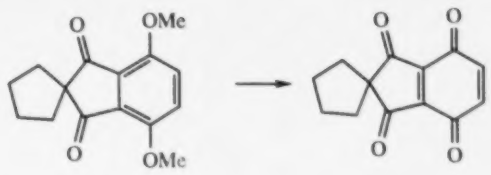
An ozone-oxygen stream was bubbled through a stirred and cooled (-78 °C) solution of spiroketone **312** (200 mg, 0.60 mmol) in CH_2Cl_2 (9 mL) until the starting material had just disappeared (3 min, TLC control, silica, 1:1 EtOAc-hexane). $(MeO)_3P$ (0.20 mL, 1.8 mmol) was injected, the cold bath was removed, and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm), using 1:1 EtOAc-hexane, gave spirodiketone **313** (154 mg, 94%) as a homogeneous (^1H NMR, 200 MHz), light yellow solid: mp 124-127 °C; FTIR (CH_2Cl_2 cast) 1795, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.93 (s, 8 H), 3.97 (s, 6 H), 7.22 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 27.34 (t'), 35.44 (t'), 56.47 (q'), 60.48 (s'), 119.71 (d'), 129.11 (s'), 150.97 (s'), 203.09 (s'); exact mass *m/z* calcd for $C_{15}H_{16}O_4$ 260.1049, found 260.1049.

4,7-Dihydroxyspiro[2*H*-indene-2,1'-cyclopentane]-1,3-dione (302).

313 **302**

BBr_3 (1.75 M in CH_2Cl_2, 0.9 mL, 1.56 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ketone **313** (45.4 mg, 0.174 mmol) in CH_2Cl_2 (3 mL). The cold bath was removed and stirring was continued overnight. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 0.1:100 AcOH-CH_2Cl_2, gave **302** (25.8 mg, 64%) as a homogeneous (^1H NMR, 300 MHz), light yellow solid: mp 157-158 °C; FTIR (CH_2Cl_2 cast) 3410, 1730, 1680, 1484 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.92 (s, 8 H), 7.17 (s, 2 H), 8.04 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 207.10 (s'), 149.59 (s'), 126.28 (d'), 122.63 (s'), 60.49 (s'), 35.2 (t'), 27.5 (t'); exact mass *m/z* calcd for $C_{13}H_{12}O_4$ 232.0736, found 232.0734.

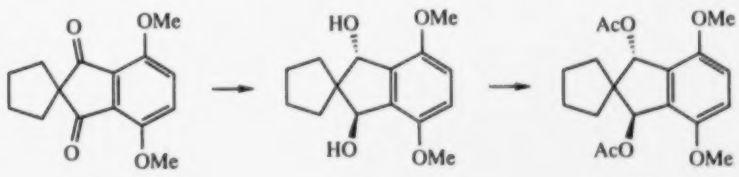
Spiro[2*H*-indene-2,1'-cyclopentane]-1,3,4,7-tetraone (303).



313 303

AgO (63 mg, 0.51 mmol) and HNO_3 (2 drops) were added to a stirred solution of diketone **313** in acetone (3 mL) at 50 °C. Stirring was continued for 30 min and the mixture was then poured into water, extracted with $CHCl_3$ (2 x 10 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:1 EtOAc-hexane, gave quinone **303** (19 mg, 65%) as a foam: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.90 (s, 8 H), 6.90 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 27.20 (t'), 35.25 (t'), 58.92 (s'), 137.09 (d'), 138.03 (s'), 184.86 (s'), 202.85 (s'). The compound decomposed before a mass spectrum was taken.

***trans*-1,3-Dihydro-4,7-dimethoxyspiro[2*H*-indene-2,1'-cyclopentane]-1,3-diol diacetate (322).**



313 321 322

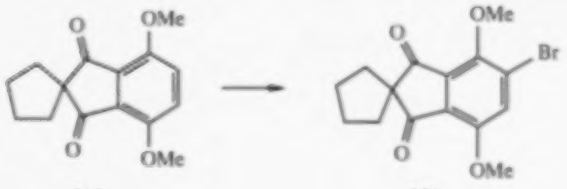
$NaBH_4$ (156 mg, 4.14 mmol) was added to a stirred and cooled (0 °C) solution of spirodiketone **313** (179 mg, 0.69 mmol) in MeOH (15.0 mL) and stirring was continued for 6 h. Saturated aqueous NH_4Cl (20 mL) was added and the mixture was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in dry CH_2Cl_2 (15.0 mL) and the solution was stirred at 0 °C for 5 min. Ac_2O (0.16 mL), pyridine (0.16 mL), and DMAP (10.0 mg) were then added, and stirring at 0 °C was continued for 3 h. Evaporation of the solvent and flash chromatography the residue over silica gel (2 x 15 cm), using 3:7 EtOAc-hexane, gave diacetate **322** (172 mg, 72%) as a clear oil composed mainly (95% by ^1H NMR) of the *trans* isomer: FTIR ($CHCl_3$ cast) 1736, 1501, 1263, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) (signals for *trans* isomer only) δ 1.38--1.89 (m, 8 H), 2.08 (s, 6 H), 3.74 (s, 6 H), 6.36 (s, 2 H), 6.72 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 21.07 (q'), 24.73 (t'), 31.30 (t'), 55.94 (q'), 58.69 (s'), 78.21 (d'), 112.11 (d'), 130.49 (s'), 150.55 (s'), 170.65 (s'); exact mass *m/z* calcd for $C_{19}H_{24}O_6$ 348.1573, found 348.1581.

trans-1,3-Bisacetoxy-1,3-dihydro[2_H_-indene-2,1'-cyclopentane]-4,7-dione (323).

322 323

A solution of $(NH_4)_2Ce(NO_3)_6$ (425 mg, 0.78 mmol) in water (2 mL) was added at room temperature to a stirred solution of diacetate **322** (136 mg, 0.39 mmol) in MeCN (10 mL). After 5 min, the mixture was poured into water (30 mL) and extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm), using 1:3 EtOAc-hexane, gave quinone **323** (98.2 mg, 80%) as a yellow solid consisting mainly (98% by ^1H NMR) of the *trans* isomer: FTIR ($CHCl_3$ cast) 1745, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.43--1.88 (m, 8 H), 2.07 (s, 6 H), 6.18 (s, 2 H), 6.71 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 20.82 (q'), 24.30 (t'), 31.13 (t'), 57.16 (s'), 77.49 (d'), 137.07 (d'), 145.96 (s'), 169.92 (s'), 184.38 (s'); exact mass *m/z* calcd for $C_{13}H_{12}O_3$ (M - $C_4H_6O_3$) (M - Ac - AcO) 216.0786, found 216.0788. Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 63.77; H, 5.68.

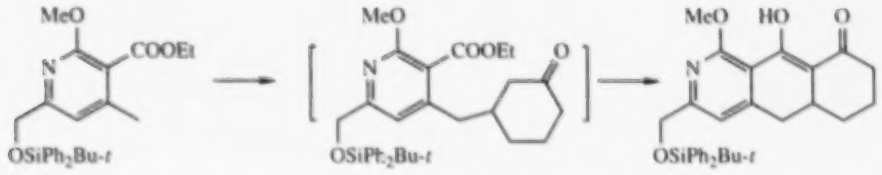
5-Bromo-4,7-Dimethoxyspiro[2*H*-indene-2,1'-cyclopentane]-1,3-dione (331).



Dibromoisocyanuric acid (14 mg, 0.049 mmol) in concentrated H_2SO_4 (1 mL) was added dropwise to a stirred solution of ketone **313** (21.1 mg, 0.081 mmol) in concentrated H_2SO_4 (2 mL). Stirring was continued at room temperature for 1 h. The mixture was poured into ice water (5 mL) and extracted with $CHCl_3$ (2 x 10 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:9 EtOAc-hexane, gave bromide **331** (12.5 mg, 45%) as a homogeneous (^1H NMR, 200 MHz), light yellow solid : mp 117.6-118.2 °C; FTIR (CH_2Cl_2 cast) 1740, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.90 (s, 8 H), 3.93 (s, 3 H), 3.96 (s, 3 H), 7.42 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 27.41 (t'), 35.61 (t'), 56.79 (q'), 60.71 (s') 62.26 (q'), 122.80 (d'), 128.04 (s'), 128.62 (s'), 133.68 (s'), 147.87 (s'), 153.26 (s'), 201.51 (s'), 202.01 (s'); exact mass *m/z* calcd for $C_{15}H_{15}{}^{79}BrO_4$ 338.0154, found 338.0155; exact mass *m/z* calcd for $C_{15}H_{15}{}^{81}BrO_4$ 340.0133, found 340.0136. Anal. Calcd for $C_{15}H_{15}BrO_4$: C, 53.12; H,

4.46. Found: C, 52.92, H, 4.70.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-5a,6,7,8-tetrahydro-10-hydroxy-1-methoxybenz[*g*]isoquinolin-9(5*H*)-one (345).



343 **344** **345**

This experiment must be done on a small scale (a maximum of 10 g of starting pyridine). Use of more concentrated solutions than specified below results in diminished yields. *n*-BuLi (1.6 M in hexane, 16.2 mL, 25.9 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-Pr_2NH (4.57 mL, 34.9 mmol) in THF (600 mL). The solution was stirred for 30 min at this temperature and a solution of ester **343**[78] (3.00 g, 6.47 mmol) in THF (16 mL) was added dropwise over 5 min. The deep orange solution was stirred for 5 min, and cyclohexenone (2.83 mL, 29.2 mmol) was then added over 30 sec. [The color of the pyridyllithium ranges from dark brown to dark green.] Stirring was continued for a further 5 min and the cold bath was removed. After 3 h, AcOH (8 mL, 140 mmol) was added and the solvents were evaporated. The residue was diluted with water (300 mL), extracted with CH_2Cl_2 (2 x 100 mL), and dried ($MgSO_4$). Evaporation of the solvent

and flash chromatography of the residue over silica gel (5 x 15 cm), using 1:5 EtOAc-hexane, gave diketone **345** (2.53 g, 76 %) as a pure (TLC, silica, 1:5 EtOAc-hexane), yellow foam: FTIR (CH_2Cl_2 cast) 1587, 1113 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 9 H), 1.28--1.43 (m, 1 H), 1.59--1.73 (m, 1 H), 1.92--2.00 (m, 1 H), 2.02--2.10 (m, 1 H), 2.41--2.49 (m, 2 H), 2.54--2.62 (m, 1 H), 2.66--2.76 (m, 1 H), 2.78--2.86 (m, 1 H), 3.96 (s, 3 H), 4.76 (dd, *J* = 14, 1.4 Hz, 2 H), 7.12 (s, 1 H), 7.37--7.48 (m, 6 H), 7.68--7.75 (m, 4 H), 8.28 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 19.35 (s'), 20.86 (t'), 26.90 (q'), 30.11 (t'), 31.15 (t'), 32.64 (d'), 37.22 (t'), 54.09 (q'), 66.39 (t'), 109.06 (s'), 112.45 (d'), 113.48 (s'), 127.84 (d'), 129.89 (d'), 133.06 (s'), 133.13 (s'), 135.53 (d'), 155.26 (s'), 161.85 (s'), 162.67 (s'), 182.27 (s'), 186.12 (s'); exact mass *m/z* calcd for $C_{27}H_{26}NO_4Si$ (M - C_4H_9) 456.1631, found 456.1625. Anal. Calcd for $C_{31}H_{35}NO_4Si$: C, 72.48; H, 6.87; N, 2.73. Found: C, 72.31; H, 6.90; N, 2.71.

If workup is done at -78 °C, the intermediate **344** can be isolated as a pure (^1H NMR, 300 MHz), clear oil: FTIR (CH_2Cl_2 cast) 2930, 1715, 1600, 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13 (s, 9 H), 1.38 (t, *J* = 6.6 Hz, 3 H), 1.40--1.78 (m, 2 H), 1.83--1.93 (m, 1 H), 1.98--2.17 (m, 3 H), 2.19--2.46 (m, 3 H), 2.64 (d, *J* = 6.0 Hz, 2 H), 3.86 (s, 3 H), 4.39 (t, *J* = 6.6 Hz, 2 H), 4.76 (s, 2 H), 7.05 (s, 1 H), 7.33--7.47 (m, 6 H), 7.67--7.76 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.27 (q'), 19.35 (s'), 25.02 (t'), 26.88 (q'), 30.93 (t'), 39.78

(d'), 39.94 (t'), 41.28 (t'), 47.94 (t'), 53.77 (q'), 61.42 (t'), 66.29 (t'), 113.68 (d'), 115.80 (s'), 127.81 (d'), 129.85 (d'), 133.22 (s'), 135.49 (d'), 149.04 (s'), 159.44 (s'), 160.32 (s'), 167.20 (s'), 210.56 (s'); exact mass *m/z* calcd for $C_{29}H_{32}NO_5Si$ (M - C_4H_9) 502.2050, found 502.2049.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-7,8-dihydro-10-hydroxy-1-methoxybenz[*g*]isoquinolin-9(6*H*)-one (346).

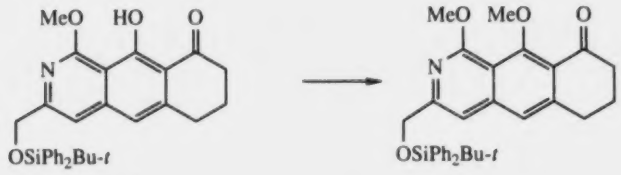
345 **346**

DDQ (1.24 g, 5.46 mmol) was added at room temperature portionwise over 30 min to a stirred solution of ketone **345** (2.53 g, 4.93 mmol) in CH_2Cl_2 (50 mL). Stirring was continued for an additional 10 min and the mixture was then filtered. Evaporation of the solvent and flash chromatography of the residue over silica gel (5 x 15 cm), using 1:5 EtOAc-hexane, gave **346** (2.10 g, 83%) as a pure (^{1}H NMR, 400 MHz), light yellow solid: mp 168.0-169.2 °C; FTIR (CH_2Cl_2 cast) 1627, 1565, 1119 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9 H), 2.07--2.17 (m, 2 H), 2.75 (t, J = 6.4 Hz, 2 H), 3.03 (t, J = 5.6 Hz, 2 H), 4.05 (s, 3 H), 4.82 (s, 2 H), 6.96 (s, 1 H), 7.35 (s, 1 H), 7.36--7.47 (m, 6 H), 7.73--7.77 (m, 4 H), 9.97

(s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.33 (s'), 22.49 (t'), 26.88 (q'), 30.21 (t'), 38.64 (t'), 53.94 (q'), 66.29 (t'), 107.87 (s'), 109.30 (d'), 112.80 (s'), 115.25 (d'), 127.76 (d'), 129.76 (d'), 133.23 (s'), 135.47 (d'), 144.23 (s'), 145.26 (s'), 156.77 (s'), 162.12 (s'), 165.76 (s'), 204.21 (s'); exact mass *m/z* calcd for $C_{27}H_{24}NO_4Si$ (M - C_4H_9) 454.1744, found 454.1475. Anal. Calcd for $C_{31}H_{33}NO_4Si$: C, 72.77; H, 6.50; N, 2.74. Found: C, 72.87; H, 6.75; N, 2.73.

This reaction can also be done in benzene, but it is then slower, and it is more difficult to isolate the product because the material for flash chromatography is too thick to be easily loaded onto the column.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-7,8-dihydro-1,10-dimethoxybenz[*g*]isoquinolin-9(6*H*)-one (347).

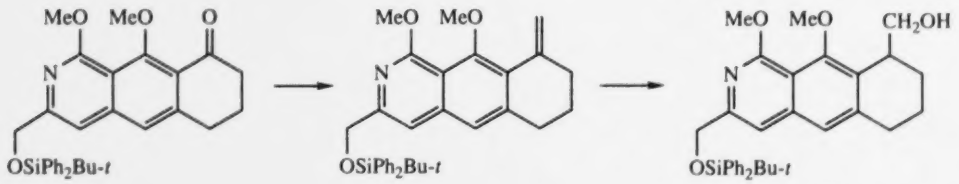


346 **347**

K_2CO_3(2.46 g, 17.8 mmol) and Me_2SO_4 (1.68 mL, 17.8 mmol) were added to a solution of naphthol **346** (1.82 g, 3.56 mmol) in acetone (40 mL), and the suspension was refluxed for 12 h. Aqueous ammonium hydroxide (10%, 20 mL) was added and the mixture was extracted with Et_2O (2 x 100 mL), washed with

brine (30 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 15 cm), using 1:3 EtOAc-hexane, gave **347** as a pure (TLC, silica, 1:3 EtOAc-hexane), yellow foam (1.50 g, 80%): FTIR (CH_2Cl_2 cast) 1620, 1350, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.16 (s, 9 H), 2.00--2.20 (m, 2 H), 2.65 (t, J = 6.6 Hz, 2 H), 3.03 (t, J = 5.8 Hz, 2 H), 3.96 (s, 3 H), 4.02 (s, 3 H), 4.82 (s, 2 H), 7.27--7.50 (m, 8 H), 7.62--7.83 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.40 (s'), 22.57 (t'), 26.93 (q'), 31.14 (t'), 41.10 (t'), 53.97 (q'), 63.25 (q'), 66.30 (t'), 109.08 (d'), 113.20 (s'), 121.10 (d'), 124.39 (s'), 127.79 (d'), 129.78 (d'), 133.37 (s'), 135.53 (d'), 143.47 (s'), 145.89 (s'), 154.53 (s'), 161.02 (s'), 161.15(s'), 196.59 (s'); exact mass m/z calcd for $C_{28}H_{26}NO_4Si$ (M - C_4H_9) 468.1631, found 468.1635. Anal. Calcd for $C_{32}H_{35}NO_4Si$: C,73.11; H, 6.71; N, 2.66. Found: C, 72.85; H, 6.64; N, 2.63.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxybenz[*g*]isoquinoline-9-methanol (349).



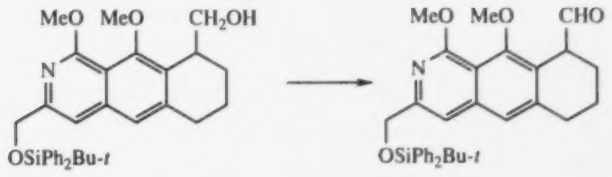
347 **348** **349**

t-BuOK (0.47 g, 95%, 4.0 mmol) was added in one portion to a stirred suspension of methyltriphenylphosphonium chloride (1.63 g, 97%, 4.6 mmol) in dry THF (10 mL). The resulting yellow suspension was stirred for 30 min and then ketone **347** (0.56 g, 1.1 mmol) in dry THF (5 mL) was added dropwise over *ca.* 1 min. The mixture turned from yellow to dark brown. Stirring at room temperature was continued for a further 30 min, and water (10 mL) was then added. The mixture was extracted with Et_2O (3 x 10 mL), and the combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using 1:20 EtOAc-hexane, gave alkene **348** (0.52 g, 93%) as a pure (^1H NMR, 200 MHz), clear oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.14 (s, 9 H), 1.83--2.00 (m, 2 H), 2.56 (t, J = 6.9 Hz, 2 H), 2.93 (br t, J = 6.9 Hz, 2 H), 3.72 (s, 3 H), 4.06 (s, 3 H), 4.83 (d, J = 1 Hz, 1 H), 5.36 (d, J = 2.4 Hz, 1 H), 6.13 (d, J = 2.4 Hz, 1 H), 7.29 (s, 1 H), 7.32--7.46 (m, 8 H), 7.71--7.82 (m, 4 H).

9-BBN (0.5 M in THF, 10 mL, 5.0 mmol) was added dropwise to a stirred solution of the above olefin (**348**) (0.52 g, 1.0 mmol) in Et_2O (5 mL). The mixture was stirred for an additional 8 h at room temperature, and aqueous NaOH (2.5 M, 20 mL, 50 mmol) was then added dropwise with stirring (H_2 evolution), followed by H_2O_2 (30%, 20 mL, 176 mmol). The mixture was stirred and refluxed vigorously for 2 h, cooled to room temperature, and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (2 x 10

mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 15 cm), using 2:3 EtOAc-hexane, gave alcohol **349** (0.51 g, 97%) as a pure (TLC, silica, 1:1 EtOAc-hexane), white foam: FTIR (CH_2Cl_2 cast) 3420, 2931, 2857, 1621, 1558, 1546, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 200.132 MHz) δ 1.22 (s, 9 H), 1.71--2.00 (m, 3 H), 2.13--2.36 (m, 1 H), 2.69--2.82 (br s, 1 H), 2.89--3.01 (m, 2 H), 3.43--3.57 (m, 1 H), 3.71 (t, J = 8.8 Hz, 1 H), 3.89 (s, 3 H), 3.90--4.02 (m, 1 H), 4.08 (s, 3 H), 4.92 (s, 2 H), 7.37 (s, 1 H), 7.38--7.52 (m, 7 H), 7.78--7.91 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 Hz) δ 16.24 (t'), 19.36 (s'), 24.65 (t'), 26.90 (q'), 29.99 (t'), 35.65 (q'), 53.77 (q'), 62.39 (d'), 66.19 (t'), 66.31 (t'), 109.5 (d'), 111.67 (s'), 122.36 (d'), 127.69 (d'), 129.15 (s'), 129.65 (d'), 133.55 (s'), 135.52 (d'), 139.71 (s'), 142.22 (s'), 150.67 (s'), 155.22 (s'), 158.67 (s'); exact mass *m/z* calcd for $C_{33}H_{39}NO_4Si$ 541.2648, found 541.2620.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxybenz[*g*]isoquinoline-9-carboxaldehyde (350).

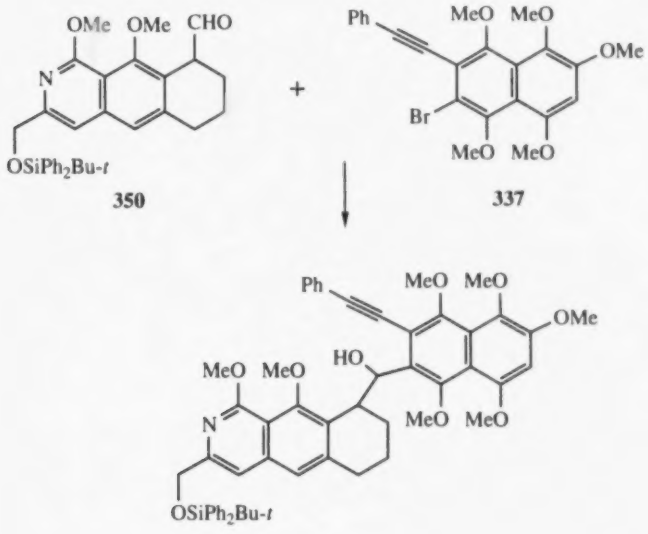


349 **350**

Dry DMSO (307 μL, 4.29 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (188 μL, 2.15 mmol) in CH_2Cl_2 (14.4 mL) under Ar. After 10 min, a solution of alcohol **349** (0.773 g, 1.43 mmol) in CH_2Cl_2 (7.2 mL) was added dropwise over *ca.* 10 min. Stirring at -78 °C was continued for 30 min, and then Et_3N (2.0 mL, 14.50 mmol) was added dropwise. After 20 min, the cold bath was removed. After a further 30 min, brine (30 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:6 EtOAc-hexane, gave aldehyde **350** (0.57 g, 74%) as a pure (^1H NMR, 200 MHz), white foam: FTIR (CH_2Cl_2 cast) 2920, 2840, 1720, 1620, 1560, 1340, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 400.134 MHz) δ 1.17 (s, 9 H), 1.75--1.92 (m, 2 H), 1.92--2.03 (m, 1 H), 2.06--2.18 (m, 1 H), 2.95 (t, *J* = 6.8 Hz, 2 H), 3.80 (s, 3 H), 3.86--3.94 (m, 1 H), 4.06 (s, 3 H), 4.85 (s, 2 H), 7.34--7.48 (m, 8 H), 7.74--7.80 (m, 4 H), 9.65 (d, *J* = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.45 (s'), 20.56 (t'), 23.77 (t'), 26.98 (q'), 29.85 (t'), 47.53 (q'), 53.89 (q'), 61.11 (d'), 66.38 (t'), 109.53 (d'), 111.67 (s'), 122.66 (d'), 124.47 (s'), 127.78 (d'), 129.75 (d'), 133.54 (s'), 133.60 (s'), 135.6 (d'), 140.43 (s'), 141.80 (s'), 151.46 (s'), 155.40 (s'), 159.00 (s'), 201.25 (d'); exact mass *m/z* calcd for $C_{33}H_{38}NO_4Si$ (M + H) 540.2570, found 540.2561. Anal. Calcd for $C_{33}H_{37}NO_4Si$: C, 73.44; H, 6.91; N, 2.60. Found:

C, 73.56; H, 6.98; N, 2.63.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxy-α-[1,4,5,6,8-pentamethoxy-3-(phenylethynyl)-2-naphthalenyl]-benz[*g*]isoquinoline-9-methanol (371).

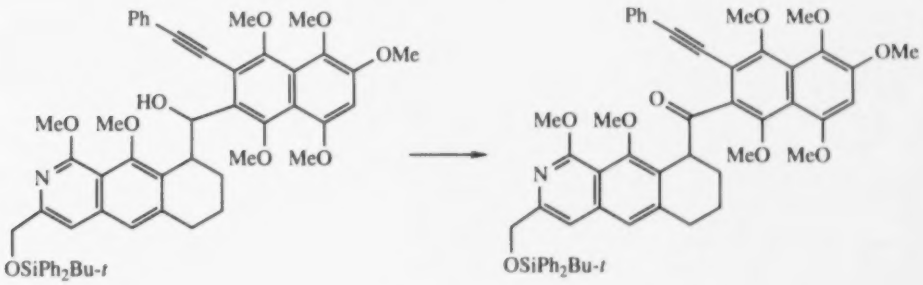


Bromonaphthalene **337** (531 mg, 1.16 mmol) was dissolved in dry THF (7.2 mL), and the solution was diluted with an equal volume of dry Et_2O and cooled to -78 °C (Ar atmosphere). *n*-BuLi (1.6 M solution in hexanes, 0.89 mL, 1.41 mmol) was added dropwise (over *ca.* 1 min) and stirring was continued for 5 min at -78 °C. A solution of aldehyde **350** (636 mg, 1.18 mmol) in dry Et_2O (7.2 mL) was then injected by syringe over *ca.* 2 min and stirring at -78 °C was continued for 45 min. The cold bath was removed and, after

15 min, saturated aqueous NH_4Cl (*ca.* 20 mL) was added. The mixture was extracted with EtOAc (1 x 50 mL, 1 x 10 mL), and the combined organic extracts were washed with brine (1 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 3:7 EtOAc-hexane, gave **371** (611 mg, 56%) as a pure (^1H NMR, 200 MHz), light yellow foam: FTIR ($CHCl_3$ cast) 2920, 1600, 1559, 1352, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 400.134 MHz) δ 1.17 (s, 9 H), 1.67--1.78 (m, 1 H), 1.80--1.91 (m, 1 H), 2.28--2.43 (m, 1 H), 2.73--2.93 (m, 2 H), 3.00--3.11 (m, 1 H), 3.38 (s, 3 H), 3.65 (s, 3 H), 3.70 (s, 6 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 3.98 (s, 3 H), 4.07--4.16 (m, 1 H), 4.41--4.57 (m, 1 H), 4.77 (s, 2 H), 5.44 (dd, *J* = 11.6, 11.6 Hz, 1 H), 6.74 (s, 1 H), 6.99 (s, 1 H), 7.22 (s, 1 H), 7.30--7.47 (m, 11 H), 7.72--7.80 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.697 MHz) (two isomers) δ 17.66 (s'), 19.99 (t'), 24.18 (t'), 26.93 (q'), 28.69 (t'), 39.27 (d'), 53.19 (d'), 53.71 (d'), 56.69 (q'), 56.76 (q'), 57.49 (q'), 61.25 (q'), 61.73 (q'), 61.86 (q'), 62.00 (q'), 62.06 (q'), 62.71 (q'), 66.27 (t'), 66.38 (t'), 84.85 (s'), 85.26 (s'), 97.98 (s'), 99.25 (d'), 109.34 (d'), 109.49 (d'), 111.28 (s'), 115.53 (s'), 116.53 (s'), 121.70 (d'), 123.52 (s'), 125.48 (s'), 127.70 (d'), 128.20 (d'), 128.33 (d'), 129.65 (d'), 130.15 (s'), 130.70 (s'), 131.18 (d'), 133.57 (s'), 133.64 (s'), 135.50 (d'), 135.54 (d'), 136.91 (s'), 137.21 (s'), 139.75 (s'), 139.95 (s'), 142.25 (s'), 143.10 (s'), 149.96 (s'), 150.08 (s'), 150.66 (s'), 150.77 (s'), 152.71 (s'), 153.59 (s'), 155.17 (s'), 159.06 (s'), 182.24 (s');

mass (HRFAB) *m/z* calcd for $C_{56}H_{60}NO_9Si$ (M + H) 918.4037, found 918.4029. Anal. Calcd for $C_{56}H_{59}NO_9Si$: C, 73.26; H, 6.48; N, 1.53. Found: C, 73.26; H, 6.59; N, 1.57.

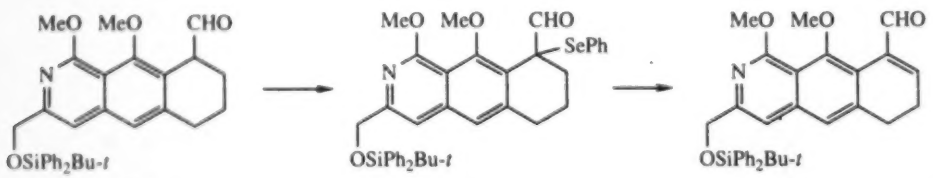
[3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxybenz[*g*]isoquinolin-9-yl][1,4,5,6,8-pentamethoxy-3-(phenylethynyl)-2-naphthalenyl]methanone (372).



Ph_3BiCO_3[106] (0.85 g, 1.71 mmol) was added to a vigorously stirred solution of alcohol **371** (0.44 g, 0.48 mmol) in a mixture of PhMe (22 mL) and pyridine (1.5 mL). The mixture was heated at 95 °C under Ar for 60 h (TLC control, silica, 40% EtOAc-hexane). The mixture was then filtered through a pad of silica gel (3 x 4 cm), using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 20 cm), using 3:7 EtOAc-hexane, gave **372** (0.41 g, 93%) as a pure (^{1}H NMR, 200 MHz), yellow foam: FTIR ($CHCl_3$ cast) 2920, 1358, 1345, 1099 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200.132 MHz) δ 1.15 (s, 9 H), 1.47--1.96 (m, 3 H), 2.01--2.38

(m, 1 H), 2.38--2.59 (m, 1 H), 2.63--3.08 (m, 2 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 3.99 (s, 3 H), 4.00 (s, 6 H), 4.01 (s, 3 H),.4.83 (s, 2 H), 5.21--5.32 (m, 1 H), 6.80 (s, 1 H), 7.23--7.52 (m, 12 H), 7.71--7.83 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.46 (s'), 20.13 (t'), 25.60 (t'), 26.98 (q'), 29.57 (t'), 47.79 (q'), 53.65 (q'), 56.76 (q'), 57.07 (q'), 62.16 (q'), 62.63 (q'), 64.35(q'), 66.42 (t'), 84.36 (s'), 98.02 (s'), 98.33 (d'), 109.70 (d'), 111.70 (s'), 113.98 (s'), 116.41 (s'), 121.65 (d'), 123.42 (s'), 126.51 (s'), 126.72 (s'), 127.76 (d'), 128.22 (d'), 128.36 (d'), 129.69 (d'), 131.07 (s'), 131.68 (d'), 133.66 (s'), 133.73 (s'), 135.61 (d'), 137.03 (s'), 140.41 (s'), 142.63 (s'), 150.43 (s'), 150.59 (s'), 151.49 (s'), 153.85 (s'), 154.48 (s'), 156.17 (s'), 159.19 (s'), 204.54 (s') (some signals overlap); mass (HRFAB) *m/z* calcd for $C_{56}H_{58}NO_9Si$ (M + H) 916.3881, found 916.3839.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7-dihydro-1,10-dimethoxybenz[*g*]isoquinoline-9-carboxaldehyde (354).

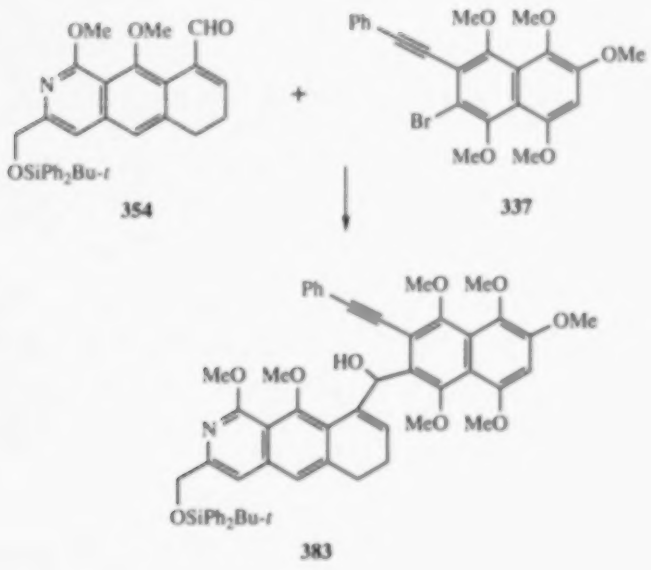


350 382 354

$PhSeNEt_2$[108a] (0.20 mL, 0.89 mmol) was added to a stirred

solution of aldehyde **350** (320 mg, 0.59 mmol) in dry CH_2Cl_2 at room temperature, and stirring was continued for 24 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm), using 1:5 EtOAc-hexane, gave selenide **382** (335 mg, 81%) as a light orange foam, which was dissolved in CH_2Cl_2 (10 mL) at 0 °C. *m*-CPBA (280 mg, 0.96 mmol) in CH_2Cl_2 (2 mL) was added and the mixture was stirred for 10 min, diluted with CH_2Cl_2 (30 mL), washed with aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:4 EtOAc-hexane, gave aldehyde **354** (160 mg, 62%) as a pure (^1H NMR, 200 MHz), light yellow foam: FTIR (CH_2Cl_2 cast) 2920, 1695, 1630, 1560, 1345, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 200.132 MHz) δ 1.14 (s, 9 H), 2.37-2.51 (m, 2 H), 2.89 (t, *J* = 6.8 Hz, 2 H), 3.64 (s, 3 H), 4.04 (s, 3 H), 4.83 (s, 2 H), 6.90 (t, *J* = 5.2 Hz, 1 H), 7.29--7.48 (m, 8 H), 7.66--7.78 (m, 4 H), 10.05 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.43 (s'), 23.11 (t'), 26.96 (q'), 28.95 (t'), 53.99 (q'), 62.40 (q'), 66.34 (t'), 109.85 (d'), 112.13 (s'), 121.49 (d'), 123.34 (s'), 127.78 (d'), 129.76 (d'), 133.48 (s'), 135.57 (d'), 137.08 (d'), 137.79 (s'), 141.13 (s'), 141.38 (s'), 152.45 (s'), 153.42 (s'), 159.40 (s'), 192.15 (d'); exact mass *m/z* calcd for $C_{29}H_{26}NO_4Si$ (M - C_4H_9) 480.1631, found 480.1625.

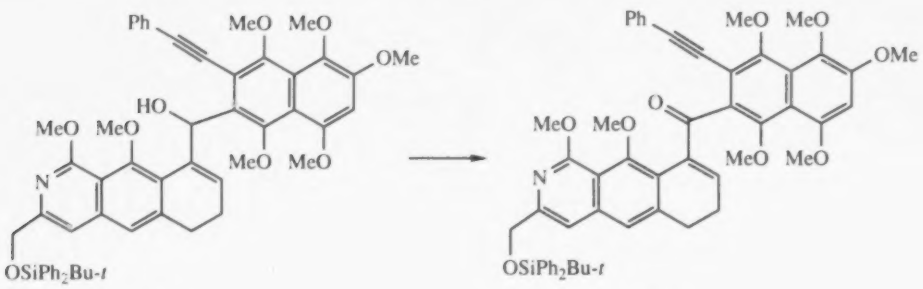
3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7-dihydro-1,10-dimethoxy-α-[1,4,5,6,8-pentamethoxy-3-(phenylethynyl)-2-naphthalenyl]benz[*g*]isoquinoline-9-methanol (383).



Bromonaphthalene **337** (136 mg, 0.298 mmol) was dissolved in dry THF (2.1 mL). The solution was diluted with an equal volume of dry Et_2O and cooled to -78 °C (Ar atmosphere). *n*-BuLi (1.6 M solution in hexane, 0.21 mL, 0.33 mmol) was added dropwise (over *ca.* 1 min) and stirring was continued for 5 min at -78 °C. A solution of aldehyde **354** (160 mg, 0.298 mmol) in dry Et_2O (2 mL) was then injected by syringe over *ca.* 2 min, and stirring at -78 °C was continued for 45 min. The cold bath was removed and, after 15 min, saturated aqueous NH_4Cl (*ca.* 5 mL) was added. The mixture was extracted with EtOAc (2 x 20 mL), and the combined organic

extracts were washed with brine (1 x 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 3:7 EtOAc-hexane, gave coupled alcohol **383** (158 mg, 58%) as a pure (TLC, silica, 2:3 EtOAc-hexane), light yellow foam: FTIR (CH_2Cl_2 cast) 3550, 2930, 1600, 1530, 1355, 1100, 1050 cm^{-1}; ^{13}C NMR ($CDCl_3$, 125.697 MHz) δ 19.46 (s'), 23.32 (t'), 28.98 (q'), 29.94 (t'), 53.86 (q'), 56.82 (q'), 57.14 (q'), 62.14 (q'), 62.31 (q'), 63.01 (q'), 63.09 (q'), 66.42 (t'), 85.94 (s'), 98.50 (d'), 99.71 (s'), 109.51 (d'), 113.04 (s'), 115.96 (s'), 116.63 (s'), 120.74 (d'), 123.43 (s'), 125.66 (s'), 125.81 (s'), 127.76 (d'), 127.77 (d'), 128.15 (d'), 129.71 (d'), 131.04 (s'), 131.33 (d'), 133.61 (s'), 135.60 (d'), 137.08 (s'), 139.66 (s'), 140.56 (s'), 144.18 (s'), 150.66 (s'), 150.73 (s'), 151.39 (s'), 153.35 (s'), 153.56 (s'), 154.90 (s'), 158.78 (s') (some of the aromatic signals overlap). Anal. Calcd for $C_{56}H_{57}O_9NSi$: C, 73.42; H, 6.27; N, 1.53. Found: C, 73.42; H, 6.27; N, 1.53. A satisfactory ^1H NMR spectrum was not obtained for this compound.

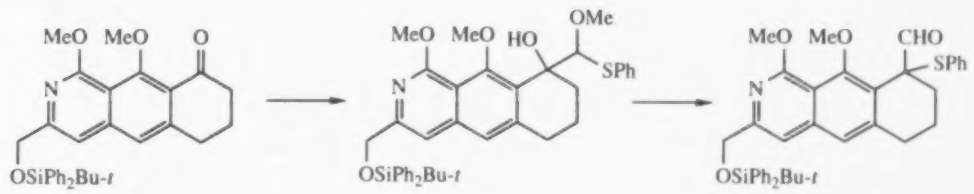
[3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7-dihydro-1,10-dimethoxybenz[*g*]isoquinolin-9-yl]-[1,4,5,6,8-pentamethoxy-3-(phenylethynyl)-2-naphthalenyl]methanone (378).



Ph_3BiCO_3[106] (301 mg, 0.61 mmol) was added to a vigorously stirred solution of alcohol **383** (158 mg, 0.172 mmol) in a mixture of PhMe (5 mL) and pyridine (0.33 mL). The mixture was heated at 90 °C under Ar for 24 h (TLC control, silica, 40% EtOAc-hexane). The mixture was then cooled and filtered through a pad of silica gel (3 x 4 cm), using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 20 cm), using 3:7 EtOAc-hexane, gave **378** (110 mg, 70%) as a pure (^{1}H NMR, 200 MHz), yellow foam: FTIR (CH_2Cl_2 cast) 2950, 1600, 1560, 1360, 1350, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (s, 9 H), 2.38--2.49 (m, 2 H), 2.90 (t, J = 6.5 Hz, 2 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 3.82 (s, 3 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 3.97 (s, 3 H), 4.06 (s, 3 H), 4.77 (s, 2 H), 6.72 (s, 1 H), 6.94 (t, J = 6.5 Hz, 1 H), 7.27--7.48 (m, 11 H), 7.53--7.64 (m, 2 H),

7.58--7.79 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.697 MHz) δ 19.44 (s'), 23.66 (t'), 26.97 (q'), 29.63 (t'), 56.65 (q'), 57.64 (q'), 62.14 (q'), 63.21 (q'), 63.96 (q'), 66.10 (t'), 85.44 (s'), 86.90 (s'), 97.68 (s'), 99.26 (s'), 109.72 (d'), 112.42 (s'), 115.68 (s'), 116.40 (s'), 120.17 (d'), 124.01 (s'), 124.87 (s'), 126.88 (s'), 127.76 (d'), 128.12 (d'), 128.22 (d'), 129.72 (d'), 129.85 (s'), 131.76 (d'), 133.52 (s'), 135.58 (d'), 137.20 (s'), 140.98 (s'), 141.12 (s'), 151.64 (s'), 151.91 (s'), 154.01 (s'), 154.07 (s'), 154.29 (s'), 159.75 (s'), 193.30 (s'), 246.02 (d') (some of the signals overlap).

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxy-9-(phenylthio)-benz[*g*]isoquinolin-9-carboxaldehyde (396).

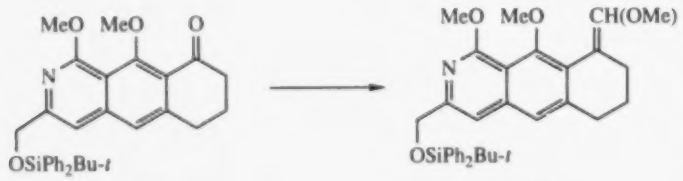


347 **397** **396**

n-BuLi (1.6 M in hexane, 0.66 mL, 1.06 mmol) was added to a stirred and cooled (-30 °C) solution of $PhSCH_2OCH_3$[115] (162 mg, 1.10 mmol) in THF (1.3 mL). The mixture was stirred for 60 min at this temperature. Ketone **347** (110 mg, 0.21 mmol) in THF (0.5 mL) was then added by cannula. The cold bath was left in place and the mixture was stirred for 3 h.

Saturated aqueous NH_4Cl (3 mL) was added. The mixture was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm), using 1:4 EtOAc-hexane, gave alcohol **397** (44 mg, 0.23 mmol) along with about 30% of starting material. The alcohol was then dissolved in PhH (2.7 mL) and toluenesulfonic acid (43.7, 0.23 mmol) was added. The solution was refluxed for 30 min, cooled, diluted with EtOAc (20 mL), washed with saturated aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:10 EtOAc-hexane, gave **396** (44 mg, 32%) as a pure (^1H NMR, 200 MHz), yellow foam, spectroscopically identical to material made from the enol ether **400**, using PhSCl (see below).

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxy-9-[(methoxy)-methylene]benz[*g*]isoquinoline (400).

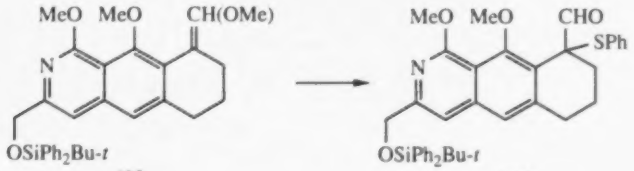


347 400

t-BuOK (4.5 g, 40.1 mmol) was added to a solution of (methoxymethyl)triphenylphosphonium chloride (15.6 g, 45.5

mmol) in THF (240 mL), and the mixture was stirred at room temperature for 30 min. Ketone **347** (6.0 g, 11.4 mmol) in THF (100 mL) was added dropwise by cannula over 10 min, and stirring was continued for 1 h after the addition. Water (120 mL) was added, and the mixture was extracted with Et_2O (2 x 300 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (10 x 15 cm), using 1:10 EtOAc-hexane, gave enol ether **400** (5.2 g, 83%) as a pure (^1H NMR, 400 MHz), light yellow solid: mp 154.8-155.8 °C; FTIR (neat) 2920, 1550, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9 H), 1.76--1.83 (m, 2 H), 2.57--2.62 (m, 2 H), 2.76--2.81 (m, 2 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 4.05 (s, 3 H), 4.81 (s, 2 H), 7.27 (s, 1 H), 7.34--7.49 (m, 8 H), 7.79--7.74 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 19.41 (s'), 22.29 (t'), 23.72 (t'), 26.93 (q'), 31.87 (t'), 53.87 (q'), 59.96 (q'), 60.35 (q'), 66.39 (t'), 109.58 (d'), 109.65 (s'), 112.68 (s'), 121.21 (d'), 126.69 (s'), 127.72 (d'), 129.67 (d'), 133.62 (s'), 135.59 (d'), 138.74 (s'), 143.57 (s'), 149.34 (d'), 150.38 (s'), 153.39 (s'), 159.24 (s'); exact mass *m/z* calcd for $C_{34}H_{39}NO_4Si$ 553.2648, found 553.2648. Anal. Calcd for $C_{34}H_{39}NO_4Si$: C, 73.74; H, 7.10; N, 2.53. Found: C, 73.77; H, 7.10: N, 2.57.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxy-9-(phenylthio)-benz[*g*]isoquinoline-9-carboxaldehyde (396).

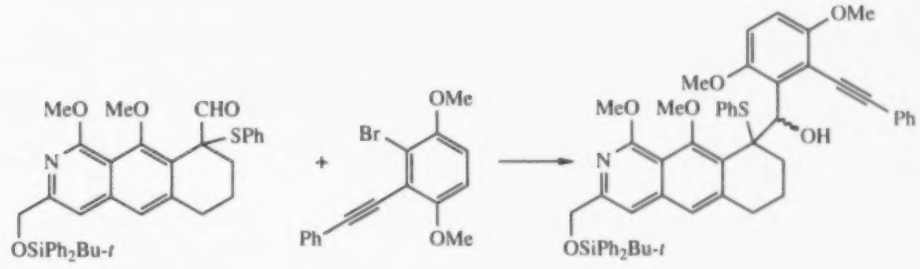


400 **396**

Enol ether **400** (577 mg, 1.04 mmol) was dissolved in CH_2Cl_2 (3 mL) at room temperature. Et_2O (58 mL) was added and the solution was cooled to -78 °C and stirred. After 5 min, CF_3COOAg (300 mg, 1.36 mmol) was added, and then PhSCl (0.155 mL, 1.18 mmol) in Et_2O (29 mL) was added dropwise by cannula over 15 min. Stirring was continued at -78 °C for 30 min after the addition. The cold bath was removed and, after 20 min, the solvent was evaporated. Flash chromatography of the residue over grade I neutral aluminum oxide (4 x 15 cm), using 1:13 EtOAc-hexane, gave aldehyde **396** (449 mg, 66%) as a pure (^{1}H NMR, 400 MHz), yellow foam: FTIR ($CHCl_3$ cast) 2950, 1715, 1623, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 9 H), 1.76--1.88 (m, 2 H), 2.01--2.10 (m, 1 H), 2.33--2.45 (m, 1 H), 2.89--3.01 (m, 1 H), 3.08--3.16 (m, 1 H), 3.96 (s, 3 H), 4.03 (s, 3 H), 4.82 (s, 2 H), 7.28--7.46 (m, 11 H), 7.60--7.65 (m, 2 H), 7.73--7.78 (m, 4 H), 10.17 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 17.83 (s'), 19.44 (t'), 26.97 (q'), 28.98 (t'), 29.45 (t'), 53.77 (q'), 62.65 (s'), 64.26 (q'),

66.31 (t'), 109.32 (d'), 111.40 (s'), 122.86 (d'), 127.12 (s'), 127.78 (d'), 128.91 (d'), 129.08 (d'), 129.76 (d'), 131.80 (s'), 133.51 (s'), 135.59 (d'), 136.82 (d'), 140.93 (s'), 141.29 (s'), 152.19 (s'), 155.46 (s'), 158.85 (s'), 198.99 (d'); exact mass *m/z* calcd for $C_{35}H_{32}NO_4SSi$ (M - C_4H_9) 590.1821, found 590.1824. Anal. Calcd for $C_{39}H_{41}NO_4SSi$: C, 72.30; H, 6.38; N, 2.16. Found: C, 71.97; H, 6.27; N, 2.17.

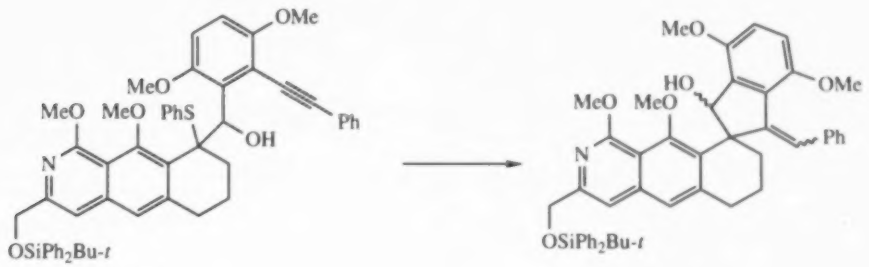
3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxy-9-(phenylthio)-α-[3,6-dimethoxy-2-(phenylethynyl)phenyl]benz[*g*]isoquinoline-9-methanol (401).



n-BuLi (1.6 M in hexane, 2.0 mL, 3.20 mmol) was added dropwise over 1 min to a stirred and cooled (-78 °C) solution of bromide **306** (0.923 g, 2.91 mmol) in Et_2O (22 mL). The mixture was stirred for an additional 30 min, and aldehyde **396** (1.72 g, 2.65 mmol) in a mixture of THF (7.7 mL) and Et_2O (7.7 mL) was then added by cannula over 5 min. Stirring was continued for 10 min after the addition. The cold bath was

removed and, after ca. 20 min, saturated aqueous NH_4Cl (20 mL) was added. The mixture was extracted with Et_2O (2 x 100 mL), and the combined organic extracts were washed with brine (30 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 15 cm), using 1:3.5 EtOAc-hexane, gave alcohol **401** (1.90 g, 81%) as a pure (^1H NMR, 400 MHz), light yellow foam: FTIR ($CHCl_3$ cast) 3500, 1620, 1556, 1475, 1105 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.18 (s, 9 H), 1.57--1.67 (m, 1 H), 1.75--1.84 (m, 1 H), 2.01--2.10 (m, 1 H), 2.32--2.41 (m, 1 H), 2.64--2.79 (m, 2 H), 3.50 (br s, 3 H), 3.86 (s, 3 H), 3.99 (s, 3 H), 4.10 (s, 3 H), 4.44 (d, J = 8.8 Hz, 1 H), 4.78 (d, J = 16Hz, 1 H), 4.84 (d, J = 16Hz, 1 H), 6.34 (d, J = 8.8 Hz, 1 H), 6.68 (d, J = 8.8 Hz, 1 H), 6.76 (d, J = 8.8 Hz, 1 H), 7.12--7.19 (m, 3 H), 7.22--7.49 (m, 15 H), 7.76--7.84 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 19.44 (s'), 20.32 (t'), 26.97 (q'), 32.00 (t'), 53.43 (q'), 55.14 (q'), 56.68 (q'), 62.92 (s'), 64.26 (q'), 66.33 (t'), 85.20 (s'), 109.08 (d'), 110.51 (d'), 111.53 (d'), 111.77 (s'), 121.05 (d'), 123.46 (s'), 127.76 (d'), 127.88 (d'), 128.04 (d'), 128.08 (d'), 128.30 (d'), 129.72 (d'), 131.00 (d'), 131.39 (d'), 133.19 (s'), 133.64 (s'), 135.09 (s'), 135.61 (d'), 136.48 (d'), 140.09 (s'), 142.05 (s'), 150.83 (s'), 151.74 (s'), 154.89 (s'), 159.05 (s') (some of the signals overlap); mass (HRFAB) *m/z* calcd for $C_{55}H_{56}NO_6SSi$ (M + H) 886.3597, found 886.3575. Anal. Calcd for $C_{55}H_{55}NO_6SSi$: C, 74.54; H, 6.26; N, 1.58. Found: C, 74.51; H, 6.30; N, 1.59.

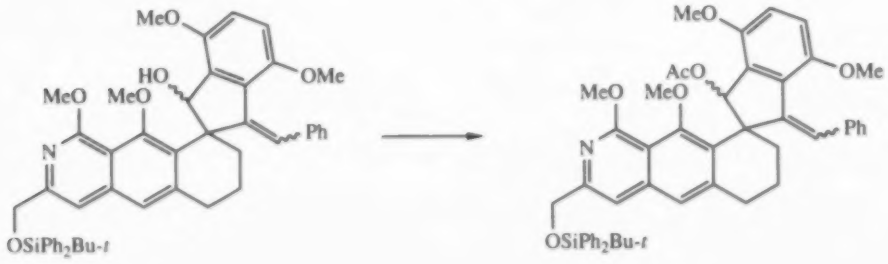
3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-3-(phenylmethylene)-1,3,6',7',8',9'-hexahydro-1',4,7,10'-tetramethoxyspiro[2*H*-indene-2,9'-benz[*g*]isoquinolin]-1-ol (403).



AIBN (10 mg, 0.061 mmol) was added to a stirred solution of alcohol **401** (1.10 g, 1.24 mmol) in PhH (23 mL). The mixture was lowered into an oil bath set at 80 °C. As soon as the solution began to reflux, solid Ph_3SnH (0.77 g, 2.19 mmol) was added in one portion. Refluxing was continued for 6 h and the mixture was then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 15 cm), using 1:4 EtOAc-hexane, gave alcohol **403** (0.84 g, 87%) as a mixture of isomers in a ratio of 10:1 (^{1}H NMR, 400 MHz): FTIR (CH_2Cl_2 cast) 3570, 1620, 1550, 1495 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (s, 9 H), 1.65--1.73 (m, 1 H), 1.76--1.84 (m, 1 H), 1.86--1.97 (m, 1 H), 2.08--2.20 (m, 1 H), 2.36-2.47 (m, 1 H), 2.71-2.82 (m, 1 H), 3.13 (s, 1 H), 3.70 (s, 3 H), 3.85 (s, 3 H), 3.92 (s, 3 H), 3.96 (s, 3 H), 4.83 (s, 2 H), 5.69 (s, 1 H), 6.61 (s, 1

H), 6.63 (s, 1 H), 6.77 (d, J = 8 Hz, 1 H), 6.86 (d, J = 8 Hz, 1 H), 6.90--7.03 (m, 3 H), 7.13 (s, 1 H), 7.34--7.47 (m, 7 H), 7.73--7.84 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.46 (s'), 20.34 (t'), 26.98 (q'), 32.02 (t'), 53.44 (q'), 55.15 (q'), 56.69 (q'), 62.92 (t'), 64.28 (q'), 66.35 (t'), 85.20 (s'), 109.09 (d'), 110.51 (d'), 111.54 (d'), 111.79 (s'), 121.07 (d'), 123.46 (s'), 127.90 (d'), 128.06 (d'), 128.10 (d'), 128.32 (d'), 129.74 (d'), 130.99 (s'), 131.41 (d'), 133.17 (s'), 133.60 (s'), 135.09 (s'), 135.63 (d'), 136.50 (d'), 140.10 (s'), 142.05 (s'), 150.67 (s'), 151.75 (s'), 154.89 (s'), 159.07 (s'), 159.27 (s') (some of the signals overlap); mass (HRFAB) m/z calcd for $C_{49}H_{52}NO_6Si$ (M + H) 778.3564, found 778.3535. Anal. Calcd for $C_{49}H_{51}NO_6Si$: C, 75.64; H, 6.61; N, 1.80. Found: C, 75.63; H, 6.64; N, 1.86.

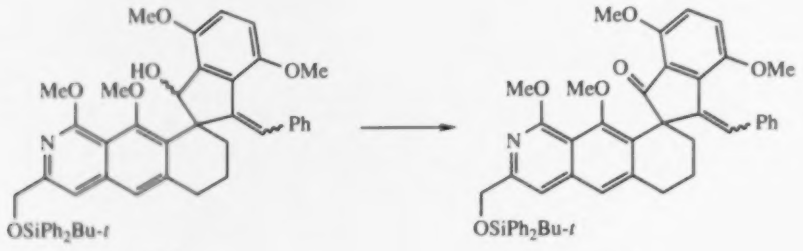
3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-3-(phenylmethylene)-1,3,6',7',8',9'-hexahydro-1',4,7,10'-tetramethoxyspiro[2*H*-indene-2,9'-benz[*g*]isoquinolin]-1-ol acetate (404).



403 404

DMAP (5 mg, 0.041 mmol) and Ac_2O (78 μL, 0.83 mmol) were added to a stirred and cooled (0 °C) solution of alcohols **403** (65 mg, 0.084 mmol) in pyridine (2 mL). Stirring was continued overnight and the mixture was evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 1:4 EtOAc-hexane, gave acetate **404** (65 mg, 95%) as a white foam [the material was a 10:1 mixture (^1H NMR, 400 MHz) of isomers]: FTIR (CH_2Cl_2 cast) 2870, 1738, 1620, 1550, 1490, 1340, ^1H NMR ($CDCl_3$, 200 MHz) δ 1.17 (s, 9 H), 1.53--1.72 (m, 2 H), 1.75--1.98 (m, 2 H), 2.03 (s, 3 H), 2.25--2.42 (m, 1 H), 2.57--2.74 (m, 1 H), 3.66 (s, 3 H), 3.78 (s, 3 H), 3.92 (s, 3 H), 3.95 (s, 3 H), 4.83 (s, 2 H), 6.55 (d, J = 7.2 Hz, 2 H), 6.70--7.01 (m, 6 H), 7.06 (s, 1 H), 7.30--7.49 (m, 7 H), 7.69--7.90 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 19.47 (s'), 21.04 (t'), 21.18 (q'), 27.00 (q'), 30.81 (t'), 32.66 (t'), 50.80 (s'), 53.48 (q'), 55.66 (q'), 62.16 (q'), 66.41 (t'), 83.72 (d'), 109.51 (d'), 110.09 (d'), 111.44 (d'), 112.05 (s'), 121.56 (d'), 125.49 (d'), 127.32 (d'), 127.78 (d'), 129.07 (d'), 129.71 (d'), 130.37 (s'), 130.93 (s'), 133.58 (s'), 133.78 (s'), 135.64 (d'), 136.04 (s'), 138.01 (s'), 139.88 (s'), 142.41 (s'), 150.27 (s'), 150.71 (s'), 150.91 (s'), 153.14 (s'), 156.72 (s'), 158.97 (s'), 170.03 (s') (two methyl signals overlap); mass (HRFAB) *m/z* calcd for $C_{51}H_{54}NO_7Si$ (M + H) 820.3669, found 820.3637.

3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6',7',8',9'-tetrahydro-1',4,7,10'-tetramethoxy-3-(phenylmethylene)spiro[2*H*-indene-2,9'-benz[*g*]isoquinolin]-1(3*H*)-one (405).

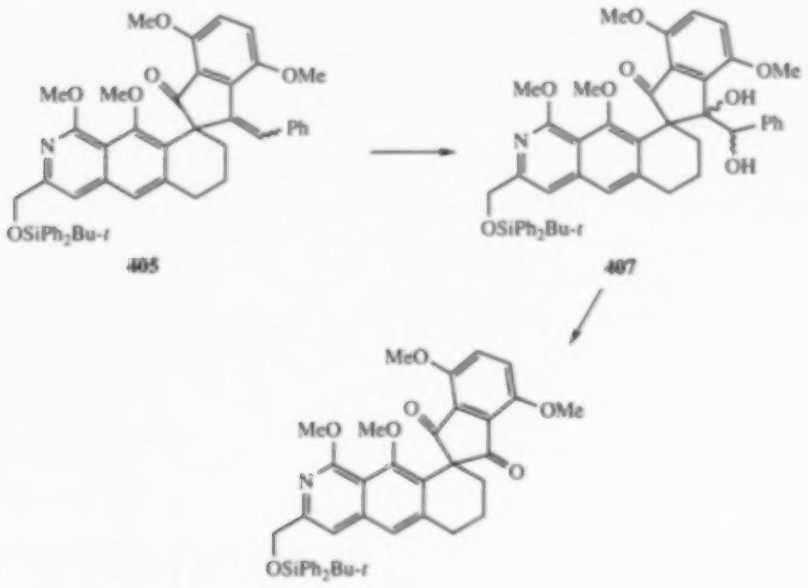


403 **405**

Ph_3BiCO_3 (1.58 g, 3.16 mmol) was added to a stirred solution of alcohols **403** (708 mg, 0.91 mmol) in a mixture of PhMe (26 mL) and pyridine (1.7 mL). The mixture was heated at 80 °C for 4.5 h, and then filtered through a pad of silica gel (3 x 5 cm), using EtOAc (200 mL). The filtrate was washed with hydrochloric acid (10%, 1 x 25 mL) and brine (1 x 25 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 15 cm), using 1:3 EtOAc-hexane, gave ketones **405** (604 mg, 85%) as a pure (TLC, silica, 2:3 EtOAc-hexane), yellow foam: FTIR ($CHCl_3$ cast) 1700, 1624, 1598, 1586, 1472, 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major isomer only) δ 1.17 (s, 9 H), 1.59--1.70 (m, 1 H), 1.96--2.25 (m, 4 H), 2.72-2.81 (m, 2 H), 3.48 (s, 3 H), 3.93 (s, 3 H), 3.94 (s, 3 H), 3.98 (s, 3 H), 4.48 (dd, J = 15, 4.5 Hz, 2 H), 6.61 (d, J = 6 Hz, 2 H), 6.83--6.93 (m, 3 H), 7.10 (s, 1 H), 7.17 (d, J = 8.4 Hz, 1 H), 7.34

(s, 1 H), 7.36--7.49 (m, 6 H), 7.72--7.83 (m, 4 H), 8.03 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 Hz) δ 19.08 (t'), 19.40 (s'), 26.95 (q'), 30.74 (t'), 34.48 (t'), 53.46 (q'), 54.36 (s'), 55.70 (q'), 56.04 (q'), 62.14 (q'), 66.38 (t'), 109.54 (d'), 110.75 (d'), 111.42 (s'), 117.54 (d'), 121.58 (d'), 122.22 (s'), 125.94 (d'), 127.35 (d'), 127.70 (d'), 128.32 (d'), 128.55 (d'), 129.66 (d'), 131.34 (s'), 133.52 (s'), 133.68 (s'), 135.57 (d'), 137.35 (s'), 137.98 (s'), 140.07 (s'), 143.68 (s'), 146.34 (s'), 150.36 (s'), 150.93 (s'), 152.40 (s'), 155.54 (s'), 158.78 (s'), 205.13 (s'); mass (HRFAB) *m/z* calcd for $C_{49}H_{50}NO_6Si$ (M + H) 776.3407, found 776.3381. Anal. Calcd for $C_{49}H_{49}NO_6Si$: C, 75.84; H, 6.36; N, 1.80. Found: C, 75.87; H, 6.26; N, 1.81.

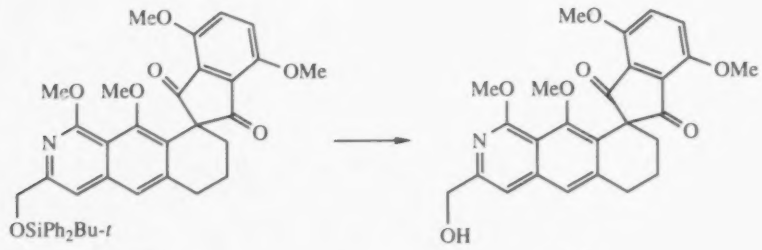
3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6',7',8',9'-tetrahydro-1',4,7,10'-tetramethoxy-spiro[2*H*-indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (406).



OsO_4 (460 mg, 1.81 mmol) was added to a stirred solution of ketones **405** (185 mg, 0.24 mmol) in pyridine (5.46 mL) under Ar. Stirring was continued for 4 h at room temperature and aqueous $NaHSO_3$ (10%, 10 mL) was then added. After 15 min, more aqueous $NaHSO_3$ (10%, 50 mL) was added and the mixture was immediately extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with 10% hydrochloric acid (2 x 10 mL) and brine (1 x 20 mL), dried ($MgSO_4$), and evaporated. The resulting crude diols **407** were dissolved in CH_2Cl_2 (12 mL). The solution was stirred, and

K_2CO_3 (98 mg, 0.709 mmol) and $Pb(OAc)_4$ (159 mg, 0.341 mmol) were added. After 30 min the solvent was evaporated, and flash chromatography of the residue over silica gel (2 x 15 cm), using 2:1 EtOAc-hexane, gave diketone **406** (104 mg, 62%) as a pure (TLC, silica, 2:3 EtOAc-hexene), yellow foam: FTIR (CH_2Cl_2 cast) 1739, 1707, 1624, 1579 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.16 (s, 9 H), 1.98--2.13 (m, 4 H), 2.95--3.12 (m, 2 H), 3.38 (s, 3 H), 3.88 (s, 3 H), 3.98 (s, 6 H), 4.79 (s, 2 H), 7.29 (s, 2 H), 7.35--7.49 (m, 8 H), 7.70--7.80 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 18.70 (t'), 19.42 (s'), 26.95 (q'), 30.23 (t'), 32.79 (t'), 53.43 (q'), 56.51 (q'), 57.44 (s'), 62.40 (q'), 66.33 (t'), 109.52 (d'), 111.14 (s'), 119.62 (d'), 122.35 (d'), 125.68 (s'), 127.67 (s'), 127.75 (d'), 129.69 (d'), 133.60 (s'), 135.58 (d'), 140.74 (s'), 143.03 (s'), 151.12 (s'), 151.33 (s'), 155.05 (s'), 158.65 (s'), 201.27 (s'); mass (HRFAB) *m/z* calcd for $C_{42}H_{44}NO_7Si$ (M + H) 702.2887, found 702.2865. Anal. Calcd for $C_{42}H_{43}NO_7Si$: C, 71.87; H, 6.18; N, 1.99. Found: C, 71.88; H, 6.19; N, 2.03.

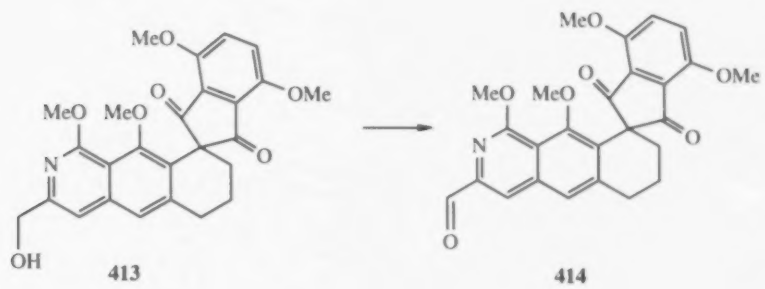
6',7',8',9'-Tetrahydro-3'-(hydroxymethyl)-1',4,7,10'-tetramethoxyspiro[2*H*-indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (413).



406 413

TBAF (1 M in THF, 0.23 mL, 0.23 mmol) was added to a stirred solution of diketone **406** (144 mg, 0.21 mmol) in THF (6.5 mL). After 40 min, the mixture was evaporated, and flash chromatography of the residue over silica gel (2 x 15 cm), using 3:1 EtOAc-hexane, gave alcohol **413** (76 mg, 80 %) as a pure (^{1}H NMR, 400 MHz), yellow solid: mp 250-255 °C; FTIR (CH_2Cl_2 cast) 3500, 1737, 1700, 1624, 1578, 1557, 1492, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98--2.10 (m, 4 H), 2.97--3.05 (2 H), 3.38 (s, 3 H), 3.97 (s, 6 H), 4.00 (s, 3 H), 4.66 (s, 2 H), 7.02 (s, 1 H), 7.28 (s, 1 H), 7.29 (s, 2 H) (OH proton was not observed); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ 18.58 (t'), 30.20 (t'), 32.66 (t'), 53.62 (q'), 56.47 (q'), 57.41 (s'), 62.44 (q'), 64.33 (t'), 109.95 (d'), 111.32 (s'), 119.65 (d'), 122.10 (d'), 126.15 (s'), 127.54 (s'), 140.51 (s'), 143.60 (s'), 149.22 (s'), 151.29 (s'), 155.13 (s'), 159.23 (s'), 201.16 (s'); exact mass *m/z* calcd for $C_{26}H_{25}NO_7$ 463.1631, found 463.1636.

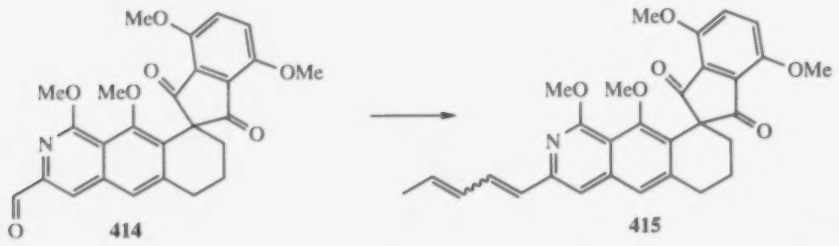
1,3,6',7',8',9'-Hexahydro-1',4,7,10'-tetramethoxy-1,3-dioxospiro[2*H*-indene-2,9'-benz[*g*]isoquinoline]-3'-carboxaldehyde (414).

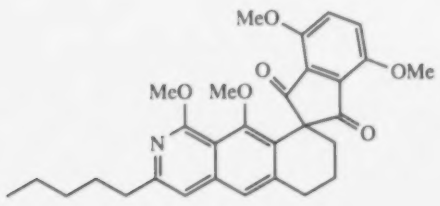


MnO_2 (100 mg, 1.15 mmol) was added in three portions at 15 minute-intervals to a stirred solution of alcohol **413** (26.5 mg, 0.57 mmol) in a mixture of CH_2Cl_2 (3 mL) and Et_2O (9 mL). After 30 min, the suspension was filtered through a pad of silica gel (2 x 3 cm), using acetone. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 2:1 EtOAc-hexene, gave aldehyde **414** (23.5 mg, 89%) as a pure (TLC, silica, 2:1 EtOAc-hexene), light yellow solid: mp 281-286 °C; FTIR (CH_2Cl_2 cast): 2941, 1738, 1704, 1610, 1578, 1555, 1492, 1275 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.98--2.18 (m, 4 H), 3.05--3.10 (m, 2 H), 3.48 (s, 3 H), 3.99 (s, 6 H), 4.13 (s, 3 H), 7.36 (s, 2 H), 7.58 (s, 1 H), 7.83 (s, 1 H), 9.98 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ 18.90 (t'), 30.47 (t'), 32.69 (t'), 54.25 (q'), 56.74 (q'), 58.16 (s'), 63.07 (q'), 114.33 (d'), 118.05 (d'), 120.44 (d'), 124.65 (s'), 127.67 (s'), 130.65 (s'), 139.26 (s'), 144.64 (s'), 145.04 (s'), 151.73 (s'), 155.38 (s'), 160.29

(s'), 192.66 (d'), 200.73 (s'); exact mass *m/z* calcd for $C_{26}H_{23}NO_7$ 461.1474, found 461.1471.

6',7',8',9'-Tetrahydro-1',4,7,10'-tetramethoxy-3'-pentylspiro[2*H*-indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (416).





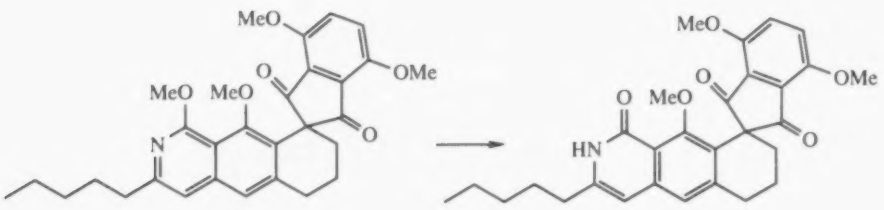
416

t-BuOK (140 mg, 1.19 mmol) was added to a stirred and cooled (0 °C) solution of (*E*)-2-butenylmethyldiphenylphosphonium iodide[133] (475 mg, 1.25 mmol) in THF (5.3 mL). After 30 min, a portion (3.4 mL) of the resulting orange-red suspension was added to a stirred solution of aldehyde **414** (134 mg, 0.29 mmol) in CH_2Cl_2 (6.3 mL) at room temperature. After 15 min, the mixture was evaporated, and flash chromatography of the residue over silica gel (2 x 15 cm),

using 2:1 EtOAc-hexane, gave diene **415** as a mixture of three isomers (^{1}H NMR, 200 MHz), which was used immediately in the next step.

Pd/C (10%, 30 mg) was added to a stirred solution of alkenes **415** in EtOAc (16 mL) under Ar. Stirring was then continued for 12 h under H_2 (balloon) at room temperature. The suspension was filtered through a pad of silica gel (3 x 2 cm), using EtOAc. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm), using 2:1 EtOAc-hexane, gave **416** (126 mg, 86%) as a pure (^{1}H NMR, 400 MHz), yellow solid: mp 181.5-182.3 °C; FTIR (CH_2Cl_2 cast) 1739, 1706, 1622, 1578, 1492, 1240 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.92 (t, *J* = 7 Hz, 3 H), 1.30--1.40 (m, 4 H), 1.73--1.82 (m, 2 H), 1.94--2.04 (m, 4 H), 2.70 (t, *J* = 8 Hz, 2 H), 2.97--3.03 (m, 2 H), 3.32 (s, 3 H), 3.98 (s, 6 H), 3.99 (s, 3 H), 6.94 (s, 1 H), 7.28 (s, 1 H), 7.33 (s, 2 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ 14.20 (q'), 19.11 (t'), 22.97 (t'), 29.04 (t'), 30.47 (t'), 31.88 (t'), 32.86 (t'), 37.71 (t'), 53.54 (q'), 56.71 (q'), 57.79 (s'), 62.59 (q'), 110.66 (s'), 111.73 (d'), 120.25 (d'), 121.73 (d'), 125.89 (s'), 127.80 (s'), 141.14 (s'), 143.25 (s'), 151.65 (s'), 153.36 (s'), 155.04 (s'), 158.86 (s'), 201.39 (s'); exact mass *m/z* calcd for $C_{30}H_{33}NO_6$ 503.2308, found 503.2307. Anal. Calcd for $C_{30}H_{33}NO_6$: C, 71.55; H, 6.61; N, 2.78. Found: C, 71.41; H, 6.54; N, 2.82.

6',7',8',9'-Tetrahydro-4,7,10'-trimethoxy-3'-pentylspiro[2*H*-indene-2,9'-benz[*g*]isoquinoline]-1,1',3-(2'*H*)-trione (418).

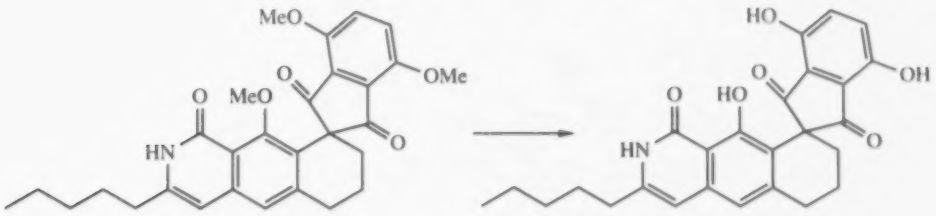


416 418

TMSCl (0.11 mL, 0.87 mmol) and NaI (22 mg, 0.15 mmol) were added to a stirred solution of **416** (56 mg, 0.11 mmol) in a mixture of CH_2Cl_2 (9 mL) and MeCN (9 mL). Stirring under Ar was continued for 1 h at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using EtOAc, gave **418** (40 mg, 74%) as a pure (^{1}H NMR, 400 MHz), yellow foam: FTIR (CH_2Cl_2 cast) 2931, 1739, 1706, 1641, 1604, 1578, 1492, 1459, 1275 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 0.81--0.87 (m, 3 H), 1.23--1.34 (m, 4 H), 1.61--1.69 (m, 2 H), 1.93--2.02 (m, 4 H), 2.47 (t, J = 8 Hz, 2 H), 2.92--2.08 (m, 2 H), 3.42 (s, 3 H), 3.97 (s, 6 H), 6.18 (s, 1 H), 7.08 (s, 1 H), 7.33 (s, 2 H), 9.82 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ 14.10 (q'), 19.00 (t'), 22.72 (t'), 27.99 (t'), 30.45 (t'), 31.42 (t'), 32.67 (t'), 33.26 (t'), 56.75 (q'), 57.51 (s'), 62.24 (q'), 103.45 (d'), 115.53 (s'), 120.24 (d'), 121.90 (d'), 126.17 (s'), 127.86 (s'), 141.01 (s'), 142.63 (s'), 146.22 (s'), 151.70 (s'),

158.62 (s'), 162.13 (s'), 201.35 (s'); exact mass *m/z* calcd for $C_{29}H_{31}NO_6$ 489.2151, found 489.2143.

6',7',8',9'-Tetrahydro-4,7,10'-trihydroxy-3'-pentylspiro[2*H*-indene-2,9'-benz[*g*]isoquinoline]-1,1',3-(2'*H*)-trione (419).

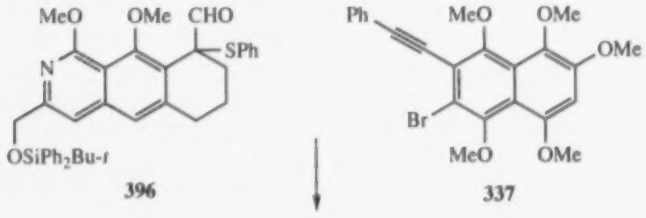


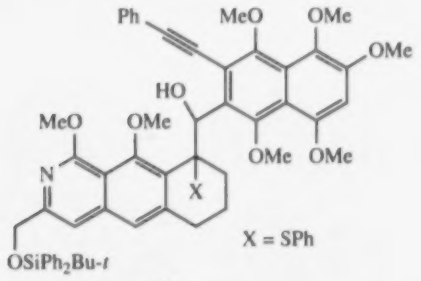
418 419

BBr_3 (1 M in CH_2Cl_2, 0.44 mL, 0.44 mmol) was added in one portion to a stirred and cooled (-78 °C) solution of **418** (21.5 mg, 0.044 mmol) in CH_2Cl_2 (3 mL). Stirring was continued at -78 °C for 2 h. The cold bath was removed and, after 2 h, water (3 mL) was added. The mixture was extracted with 200:1 $CHCl_3$-AcOH (2 x 25 mL) and the combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:35:64 AcOH-EtOAc-hexane, gave **419** (12.3 mg, 63%) as a pure (^1H NMR, 400 MHz), yellow solid: mp 285.5-288.0 °C; FTIR ($CHCl_3$ cast) 3417, 2930, 1684, 1661, 1640, 1625, 1160 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.86 (t, *J* = 7 Hz, 3 H), 1.23--1.36 (m, 4 H), 1.55--1.68 (m, 2 H), 1.97--2.28 (m, 4 H), 2.47 (t, *J* = 8 Hz,

2 H), 2.95 (t, J = 7 Hz, 2 H), 6.26 (s, 1 H), 6.82 (s, 1 H), 7.21 (s, 2 H), 7.99 (s, 2 H), 8.87 (s, 1 H) (the OH signal was not observed); ^{13}C NMR (C_2D_6SO, 100.614 MHz) δ 13.83 (q'), 18.43 (t'), 21.79 (t'), 27.56 (t'), 29.73 (t'), 30.49 (t'), 31.84 (t'), 32.09 (t'), 56.24 (s'), 103.92 (d'), 107.41 (s'), 114.81 (d'), 116.62 (s'), 123.35 (s'), 126.01 (d'), 137.39 (s'), 142.16 (s'), 146.89 (s'), 148.31 (s'), 158.03 (s'), 166.67 (s'), 201.42 (s'); exact mass m/z calcd for $C_{26}H_{25}NO_6$ 447.1682, found 447.1673.

3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6,7,8,9-tetrahydro-1,10-dimethoxy-9-(phenylthio)-α-[1,4,5,6,8-pentamethoxy-3-(phenylethynyl)-2-naphthalenyl]benz[*g*]isoquinoline-9-methanol (420).



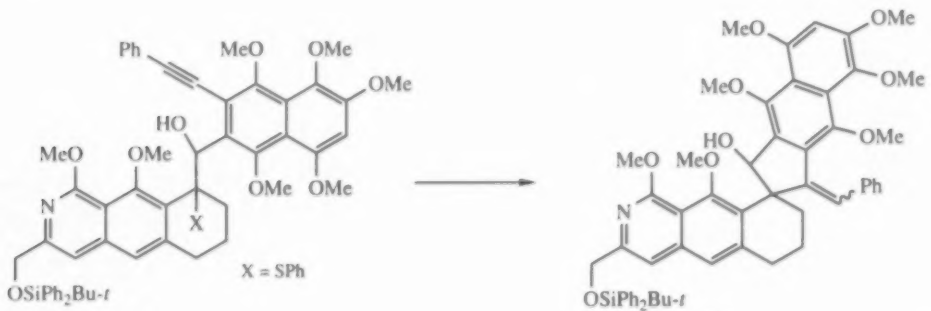


n-BuLi (1.6 M in hexane, 2.35 mL, 3.76 mmol) was added

dropwise over 1 min to a stirred and cooled (-78 °C) solution of bromide **337** (1.41 g, 3.08 mmol) in a mixture of THF (20 mL) and Et_2O (20 mL). After 10 min, aldehyde **396** (2.05 g, 3.16 mmol), in a mixture of THF (5 mL) and Et_2O (15 mL), was added over 5 min. Stirring was continued for 15 min. The cold bath was then removed and, after 5 min, saturated aqueous NH_4Cl (20 mL) was added. The mixture was extracted with Et_2O (2 x 100 mL) and the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 1:3 EtOAc-hexane, gave alcohol **420** (2.38 g, 75%) as a pure (^1H NMR, 400 MHz), light yellow foam: FTIR ($CHCl_3$ cast) 3525, 2999, 1621, 1572, 1491, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9 H), 1.52 (br s, 1 H), 1.85 (br s, 1 H), 2.18--2.28 (m, 1 H), 2.40--2.51 (m, 1 H), 2.57 (br s, 1 H), 2.65--2.74 (m, 1 H), 2.99 (br s, 3 H), 3.65 (s, 3 H), 3.83 (s, 3 H), 3.93 (s, 3 H), 3.98 (s, 3 H), 4.06 (s, 3 H), 4.11 (s, 3 H), 4.82 (s, 2 H), 6.69 (s, 2 H), 6.97 (s, 1 H), 7.12--7.23 (m, 3 H), 7.27--7.47 (m, 12 H), 7.59--7.70 (m, 2 H), 7.72--7.83 (m, 4 H) (the OH signal was not observed); ^{13}C NMR ($CDCl_3$, 125.697 MHz) δ 19.44 (s'), 19.46 (t'), 20.13 (t'), 26.5 (q'), 32.20 (t'), 53.32 (q'), 56.54 (q'), 59.71 (q'), 61.97 (q'), 62.01 (q'), 63.96 (s'), 64.20 (q'), 66.39 (t'), 108.88 (d'), 111.98 (s'), 117.50 (s'), 120.43 (d'), 123.30 (s'), 125.37 (s'), 127.75 (d'), 128.14 (d'), 128.35 (d'), 128.40 (d'), 129.71 (d'), 129.72 (d'), 131.32 (d'), 133.61 (s'), 133.69 (s'), 134.89 (s'), 135.09 (d'), 135.59 (d'),

137.41 (d'), 137.83 (s'), 140.11 (s'), 150.52 (s'), 150.70 (s'), 153.43 (s'), 159.28 (s') (several of the signals overlap); mass (HRFAB) *m/z* calcd for $C_{62}H_{64}NO_9SSi$ (M + H) 1026.4071, found 1026.4007. Anal. Calcd for $C_{62}H_{63}NO_9SSi$: C 72.56, H 6.19, N 1.36. Found: C 72.66, H 6.31, N 1.38.

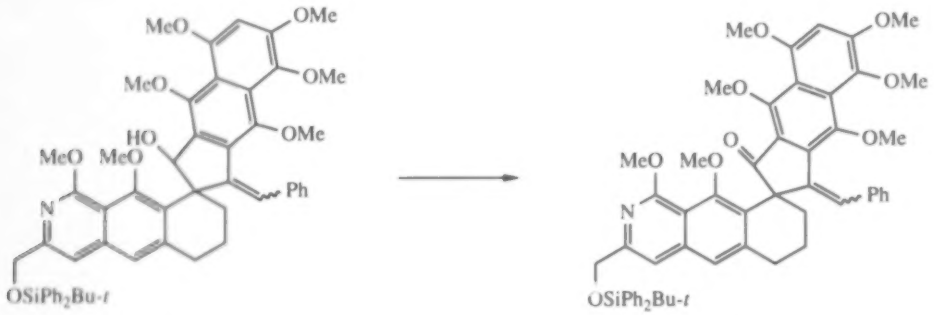
3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-1,3,6',7',8',9'-hexahydro-1',4,5,6,8,9,10'-heptamethoxy-3-(phenylmethylene)spiro[2*H*-benz[f]indene-2,9'-benz[*g*]isoquinolin]-1-ol (422).



Et_3B (1 M in hexane, 118 mL, 118 mmol) was added to a stirred solution of Ph_3SnH (7.9 mL, 30.92 mmol) and alcohol **420** (3.00 g, 2.92 mmol) in PhH (75 mL) in an open flask, stirring was continued for 30 min. Evaporation of the solvent and flash chromatography of the residue over silica gel (5 x 15 cm), using 1:2 EtOAc-hexane, gave alcohols **422** (2.12 g, 79%) as a pure (^1H NMR, 400 MHz), yellow foam: FTIR (CH_2Cl_2 cast) 3220, 2920, 1340 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (s, 9 H), 1.67--1.75 (m, 1 H), 1.80--2.06 (m, 2 H),

2.20--2.35 (m, 2 H), 2.80 (d, J = 17.8 Hz, 1 H), 3.51 (s, 1 H), 3.68 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 3.93 (s, 3 H), 4.01 (s, 3 H), 4.02 (s, 3 H), 4.80 (s, 2 H), 5.72 (s, 1 H), 6.73 (d, J = 7.2 Hz, 2 H), 6.79 (s, 1 H), 6.89--7.03 (m, 3 H), 7.15 (s, 1 H), 7.32 (s, 1 H), 7.35--7.50 (m, 6 H), 7.76--7.83 (m, 4 H), 8.03 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 19.66 (s'), 22.18 (t'), 27.11 (q'), 31.35 (t'), 32.89 (t'), 52.64 (s'), 53.45 (q'), 57.10 (q'), 57.37 (q'), 60.91 (q'), 62.05, (q'), 62.23 (q'), 62.44 (q'), 66.87 (t'), 84.44 (d'), 97.94 (d'), 109.92 (d'), 112.20 (s'), 117.93 (s'), 121.65 (d'), 125.93 (d'), 126.16 (d'), 127.61 (d'), 128.12 (d'), 129.43 (d'), 130.12 (d'), 131.22 (s'), 134.08 (s'), 134.22 (s'), 135.99 (d'), 138.15 (s'), 140.11 (s'), 140.32 (s'), 142.87 (s'), 143.61 (s'), 148.46 (s'), 149.48 (s'), 150.55 (s'), 152.59 (s'), 153.42 (s'), 156.67 (s'), 159.29 (s') (some of the peaks overlap); mass (HRFAB) *m/z* calcd for $C_{56}H_{59}NO_9Si$ 917.3959, found 917.3861. Anal. Calcd for $C_{56}H_{59}NO_9Si$: C 73.26, H 6.48, N 1.53. Found: C 73.12, H 6.63, N 1.57.

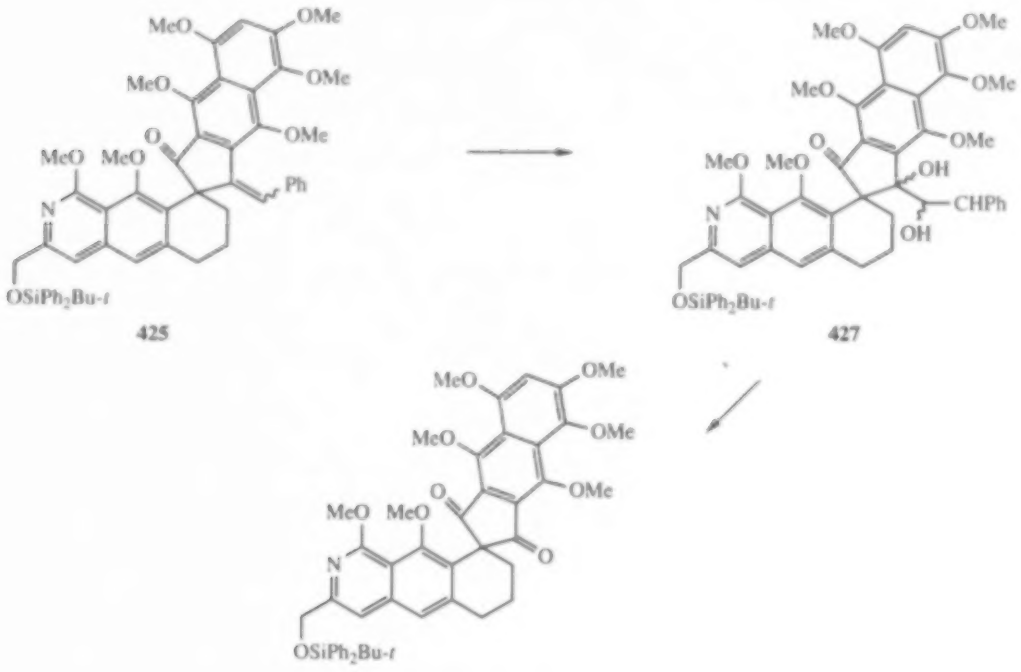
3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6',7',8',9'-tetrahydro-1',4,5,6,8,9,10'-heptamethoxy-3-(phenylmethylene)spiro[2*H*-benz[*f*]indene-2,9'-benz[*g*]isoquinolin]-1(3*H*)-one (425).



Ph_3BiCO_3 (3.2 g, 6.40 mmol) was added to a stirred solution of alcohols **422** (1.60 g, 1.74 mmol) in a mixture of PhMe (43 mL) and pyridine (2.8 mL). The mixture was heated at 90 °C for 3 h, and then filtered through a pad of silica gel (3 x 5 cm), using EtOAc (500 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 15 cm), using 2:3 EtOAc-hexane, gave ketones **425** (1.4 g, 88%) as a pure (TLC, silica, 2:3 EtOAc-hexene), yellow foam: FTIR (CH_2Cl_2 cast) 2931, 1572, 1345 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (s, 9 H), 1.65--1.78 (m, 1 H), 1.98--2.14 (m, 3 H), 2.23--2.39 (m, 1 H), 2.92 (d, *J* = 15.6 Hz, 1 H), 3.47 (s, 3 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 3.93 (s, 3 H), 3.98 (s, 3 H), 4.02 (s, 3 H), 4.05 (s, 3 H), 4.76 (d, *J* = 15.6 Hz, 1 H), 4.76 (d, *J* = 15.6 Hz, 1 H), 4.83 (d, *J* = 15.6 Hz, 1 H), 6.68 (d, *J* = 9 Hz, 1 H), 6.77 (s, 1 H), 6.80--6.98

(m, 3 H), 7.06 (s, 1 H), 7.29 (s, 1 H), 7.35--7.48 (m, 6 H), 7.72--7.81 (m, 4 H), 8.18 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ 19.66 (t'), 27.13 (q'), 30.95 (t'), 35.16 (t'), 53.44 (q'), 55.70 (s'), 56.99 (q'), 57.37 (q'), 60.87 (q'), 62.16 (q'), 62.42 (q'), 62.80 (q'), 66.89 (t'), 97.71 (d'), 109.92 (d'), 111.67 (s'), 118.3 (s'), 121.20 (s'), 121.58 (d'), 126.27 (d'), 127.68 (d'), 127.77 (d'), 128.13 (d'), 128.84 (d'), 130.12 (d'), 131.05 (s'), 134.01 (s'), 134.10 (s'), 134.39 (s'), 135.97 (d'), 137.97 (s'), 140.44 (s'), 144.07 (s'), 146.22 (s'), 148.39 (s'), 150.83 (s'), 153.43 (s'), 154.84 (s'), 155.58 (s'), 156.92 (s'), 159.21 (s'), 204.29 (s') (some of the signals overlap); mass (HRFAB) *m/z* calcd for $C_{56}H_{58}NO_9Si$ (M + H) 916.3881, found 916.3870. Anal. Calcd for $C_{56}H_{57}NO_9Si$: C 73.42, H 6.27, N 1.53. Found: C 73.36, H 6.23, N 1.57.

3'-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-6',7',8',9'-tetrahydro-1',4,5,6,8,9,10'-heptamethoxyspiro[2*H*-benz[*f*]indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (426).



OsO_4 (1.0 g, 3.93 mmol) and $MeSO_2NH_2$ (0.30 g, 3.15 mmol) were added to a stirred solution of ketone **425** (440 mg, 0.48 mmol) in pyridine (8.1 mL) under Ar. Stirring was continued for 9 h at room temperature. Pyridine (10 mL) and 10% aqueous $NaHSO_3$ (20 mL) were added and stirring was continued for 30 min. More 10% aqueous $NaHSO_3$ (200 mL) was added and the mixture was immediately extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with 10%

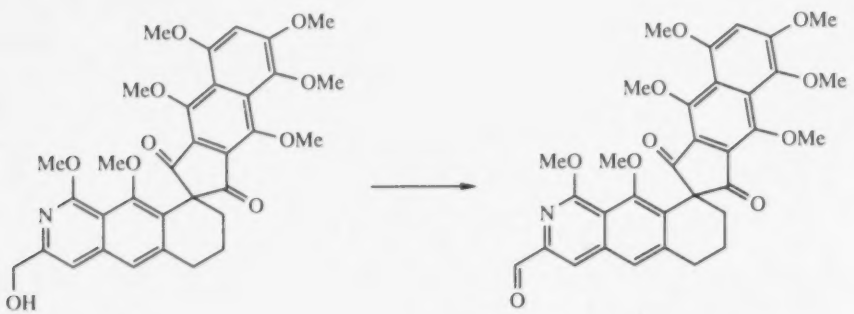
hydrochloric acid (2 x 50 mL), and brine (1 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:3 EtOAc-hexane, gave diols **427**, which were dissolved in CH_2Cl_2 (3.7 mL). The solution was stirred and K_2CO_3 (17 mg, 0.123 mmol) and $Pb(OAc)_4$ (55.1 mg, 0.124 mmol) were added. Stirring was continued for 30 min, and the suspension was then evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:3 EtOAc-hexane, gave diketone **426** (40.6 mg, 10%) as a pure (^1H NMR, 400 MHz), yellow foam: FTIR (CH_2Cl_2 cast) 2933, 1732, 1705, 1624, 1596, 1359, 1344 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.15 (s, 9 H), 1.97--2.13 (m, 4 H), 3.06--3.13 (m, 2 H), 3.19 (s, 3 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 4.01 (s, 3 H), 4.02 (s, 3 H), 4.08 (s, 6 H), 4.82 (s, 2 H), 6.94 (s, 1 H), 7.38--7.50 (m, 8 H), 7.73--7.82 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ 19.06 (t'), 19.60 (s'), 27.05 (q'), 30.53 (t'), 33.14 (t'), 53.71 (q'), 56.91 (q'), 57.57 (q'), 59.47 (s'), 62.14 (q'), 62.74 (q'), 63.10 (q'), 63.31 (q'), 66.03 (s'), 66.76 (t'), 100.08 (d'), 109.87 (d'), 111.40 (s'), 121.30 (s'), 122.37 (d'), 123.48 (s'), 126.57 (s'), 127.04 (s'), 128.11 (d'), 130.08 (d'), 131.43 (s'), 133.96 (s'), 135.92 (d'), 139.75 (s'), 140.97 (s'), 143.60 (s'), 151.54 (s'), 154.09 (s'), 154.39 (s'), 154.96 (s'), 157.05 (s'), 159.07 (s') (some of the signals overlap); mass (HRFAB) *m/z* calcd for $C_{49}H_{52}NO_{10}Si$ (M + H) 842.3360, found 842.3342.

6',7',8',9'-Tetrahydro-3'-(hydroxymethyl)-1',4,5,6,8,9,10'-heptamethoxyspiro[2*H*-benz[*f*]indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (441).

TBAF (1 M in THF, 75 μL, 0.075 mmol) was added to a stirred solution of diketone **426** (56 mg, 0.067 mmol) in THF (2.1 mL). After 40 min, the mixture was evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:1 EtOAc-hexane, gave alcohol **441** (29.5 mg, 74 %) as a pure (^{1}H NMR, 400 MHz), yellow foam: FTIR (CH_2Cl_2 cast) 3500, 1732, 1702, 1651, 1624, 1596, 1557, 1340 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.97--2.10 (m, 4 H), 2.95 (t, *J* = 6 Hz, 1 H), 3.02--3.08 (m, 2 H), 2.79 (s, 3 H), 3.89 (s, 3 H), 3.99 (s, 3 H), 4.02 (s, 6 H), 4.06 (s, 6 H), 4.63 (d, *J* = 6 Hz, 2 H), 6.94 (s, 1 H), 7.09 (s, 1 H), 7.36 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ 18.99 (t'), 30.53 (t'), 33.10 (t'), 53.89 (q'), 56.91 (q'), 57.56 (q'), 59.46 (s'), 62.13 (q'), 62.78 (q'), 63.09 (q'), 63.31 (q'), 64.76 (t'), 100.10 (d'), 110.09 (d'), 111.57 (s'), 121.29 (s'), 122.17 (d'), 123.44 (s'), 126.52 (s'), 127.38 (s'), 131.43 (s'), 139.76 (s'), 140.85

(s'), 144.05 (s'), 150.36 (s'), 151.56 (s'), 154.12 (s'), 154.41 (s'), 155.06 (s'), 157.05 (s'), 159.60 (s'), 200.35 (s'), 201.21 (s'); exact mass *m/z* calcd for $C_{33}H_{33}NO_{10}$ 603.2104, found 603.2105.

1,3,6',7',8',9'-Hexahydro-1',4,5,6,8,9,10'-heptamethoxy-1,3-dioxospiro[2*H*-benz[*f*]indene-2,9'-benz[*g*]isoquinoline]-3'-carboxaldehyde (442).

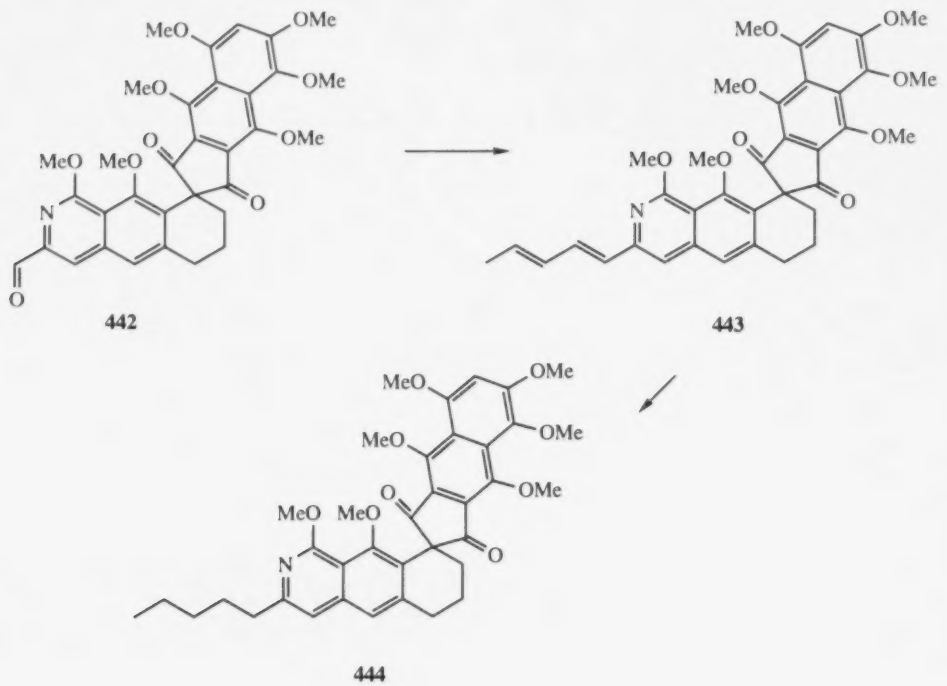


441 **442**

MnO_2 (80 mg, 0.92 mmol) was added in three equal portions at 15 minute-intervals to a stirred solution of alcohol **441** (28.0 mg, 0.046 mmol) in Et_2O (10 mL). After an additional 30 min, the suspension was filtered through a pad of silica gel (2 x 3 cm), using EtOAc (50 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 2:1 EtOAc-hexane, gave aldehyde **442** (18.2 mg, 65%) as a pure (^{1}H NMR, 400 MHz), light yellow foam: FTIR (CH_2Cl_2 cast) 2932, 1732, 1703, 1594, 1556, 1360, 1340, 1030 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.99--2.14 (m, 4 H), 3.07--3.15 (m, 2 H), 3.43 (s, 3 H), 3.90 (s, 3 H), 3.99

(s, 3 H), 4.02 (s, 3 H), 4.05 (s, 6 H), 4.10 (s, 3 H), 6.93 (s, 1 H), 7.61 (s, 1 H), 7.83 (s, 1 H), 9.99 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ 18.88 (t'), 30.54 (t'), 32.98 (t'), 54.23 (q'), 56.93 (q'), 57.56 (q'), 59.81 (s'), 62.15 (q'), 63.12 (q'), 63.35 (q'), 100.13 (d'), 114.42 (s'), 118.15 (d'), 121.27 (s'), 123.23 (s'), 124.59 (d'), 126.45 (s'), 131.25 (s'), 131.46 (s'), 139.28 (s'), 139.78 (s'), 144.62 (s'), 145.06 (s'), 151.72 (s'), 154.25 (s'), 154.60 (s'), 155.24 (s'), 157.11 (s'), 160.37 (s'), 192.70 (d'), 199.87 (s'), 200.75 (s') (two of the methyl signals overlap); exact mass *m/z* calcd for $C_{33}H_{31}NO_{10}$ 601.1948, found 601.1945.

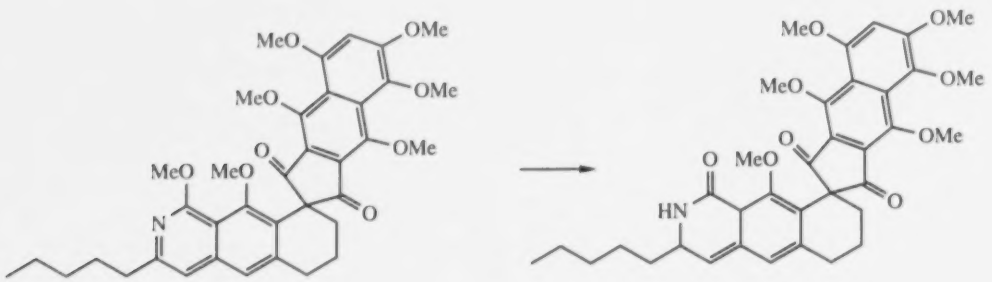
6',7',8',9'-Tetrahydro-1',4,5,6,8,9,10'-heptamethoxy-3'-pentylspiro[2*H*-benz[*f*]indene-2,9'-benz[*g*]isoquinoline]-1,3-dione (444).



t-BuOK (14 mg, 0.125 mmol) was added to a stirred suspension of (*E*)-2-butenylmethyldiphenylphosphonium iodide[133] (47 mg, 0.123 mmol) in THF (0.5 mL), and the mixture was stirred at room temperature for 20 min. A portion of the resulting orange-red suspension (0.4 mL) was then added to a stirred solution of aldehyde **442** (13 mg, 0.022 mmol) in THF (1 mL). After 5 min, the mixture was evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 3:2 EtOAc-hexane, gave diene **443** as a mixture of three isomers, which was used immediately in the next step.

Pd/C (10%, 3 mg) was added to a stirred solution of alkenes **443** in EtOAc (1 mL) under Ar. Stirring was continued under H_2 (balloon) overnight at room temperature. The suspension was filtered through a pad of silica gel (3 x 2 cm), using EtOAc. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 3:2 EtOAc-hexane, gave **444** (10.4 mg, 75%) as a pure (^{1}H NMR, 400 MHz), yellow foam: FTIR (CH_2Cl_2 cast) 2933, 2854, 1734, 1703, 1600, 1350, 1340, 1050 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.91 (t, *J* = 7.8 Hz, 3 H), 1.30--1.41 (m, 4 H), 1.74--1.81 (m, 2 H), 1.95--2.09 (m, 4 H), 2.71 (t, *J* = 7.8 Hz, 2 H), 2.98--3.05 (m, 2 H), 3.39 (s, 3 H), 3.87 (s, 3 H), 3.98 (s, 3 H), 3.99 (s, 3 H), 4.02 (s, 3 H), 4.05 (s, 6 H), 6.95 (s, 2 H), 7.33 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ 14.21 (q'), 19.07 (t'), 22.97 (t'), 29.04 (t'), 30.51 (t'), 31.87 (t'), 33.14 (t'), 37.7 (t'), 56.90 (q'), 57.56 (q'), 59.42 (s'), 62.13 (q'), 62.63 (q'), 63.08 (q'), 63.29 (q'), 100.06 (d'), 110.72 (s'), 111.75 (d'), 121.30 (s'), 121.65 (d'), 123.49 (s'), 126.43 (s'), 126.58 (s'), 131.41 (s'), 139.74 (s'), 141.14 (s'), 143.24 (s'), 151.50 (s'), 153.26 (s'), 154.05 (s'), 154.34 (s'), 154.82 (s'), 157.03 (s'), 158.90 (s'), 200.51 (s'), 201.37 (s') (two methyl signals overlap); exact mass *m/z* calcd for $C_{37}H_{41}NO_9$ 643.2781, found 643.2770.

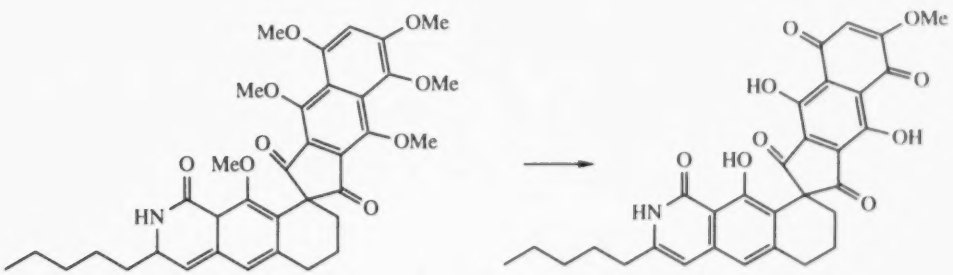
6',7',8',9'-Tetrahydro-4,5,6,8,9,10'-hexamethoxy-3'-pentylspiro[2*H*-benz[*f*]indene-2,9'-benz[*g*]isoquinoline]-1,1',3(2*H*)-trione (445).



TMSCl (12 μL, 0.095 mmol) and NaI (4.0 mg, 0.027 mmol) were added to a stirred solution of **444** (7.0 mg, 0.011 mmol) in a mixture of dry CH_2Cl_2 (1 mL) and dry MeCN (1 mL). Stirring under Ar was continued for 1 h at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using EtOAc, gave **445** (5.7 mg, 83%) as pure (^{1}H NMR, 400 MHz), yellow foam: FTIR (CH_2Cl_2 cast) 2931, 1734, 1703, 1642, 1601, 1595, 1540, 1360 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.85 (t, *J* = 7.6 Hz, 3 H), 1.24--1.35 (m, 4 H), 1.55--1.70 (m, 2 H), 1.93--2.06 (m, 4 H), 2.45 (t, *J* = 8.4 Hz, 2 H), 2.92--2.99 (m, 2 H), 3.46 (s, 3 H), 3.88 (s, 3 H), 3.98 (s, 3 H), 4.01 (s, 3 H), 4.05 (s, 6 H), 6.16 (s, 1 H), 6.94 (s, 1 H), 7.09 (s, 1 H), 8.75 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ 13.98 (q'), 18.93 (t'), 22.68 (t'), 27.99 (t'), 30.47 (t'), 31.42 (t'), 32.89 (t'), 33.27 (t'), 56.91 (q'), 57.54 (q'), 59.16 (s'), 62.11 (q'),

62.29 (q'), 63.11 (q'), 63.32 (q'), 100.10 (d'), 103.50 (d'), 115.58 (s'), 121.30 (s'), 121.83 (d'), 123.56 (s'), 126.60 (s'), 126.78 (s'), 131.36 (s'), 139.75 (s'), 140.97 (s'), 142.46 (s'), 146.20 (s'), 151.49 (s'), 154.00 (s'), 154.29 (s'), 157.00 (s'), 158.39 (s'), 162.13 (s'), 200.40 (s'), 201.28 (s'); exact mass *m/z* calcd for $C_{36}H_{39}NO_9$ 629.2625, found 629.2602.

6',7',8',9'-Tetrahydro-4,9,10'-trihydroxy-6-methoxy-3'-pentylspiro[2*H*-benz[*f*]-indene-2,9'-benz[g]iso-quinoline]-1,1',3,5,8(2'H)-pentone (335).

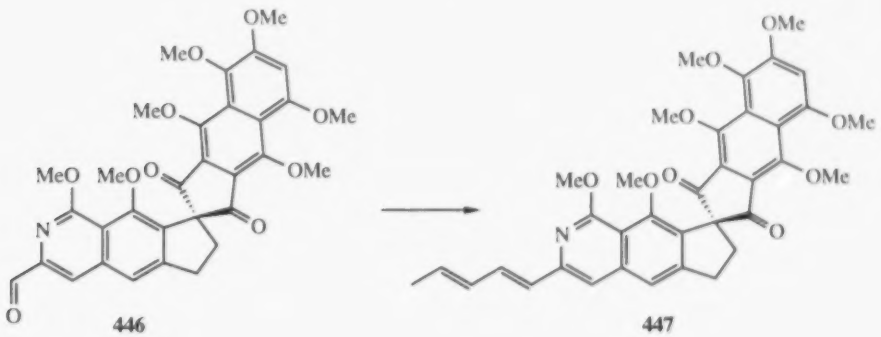


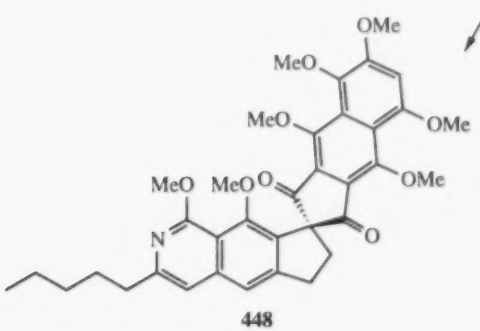
The precursor (**445**) must be freshly purified by flash chromatography before the reaction, otherwise the product will be very difficult to purify.

BBr_3 (0.53 M in CH_2Cl_2, 0.12 mL, 0.063 mmol) was added in one portion to a stirred and cooled (-78 °C) solution of **445** (4.0 mg, 0.0064 mmol) in dry CH_2Cl_2 (0.66 mL) under Ar. The solution became red-purple immediately. Stirring was continued for 1 h, and the dry-ice cold bath was changed to

an ice bath. After 10 min, water (0.5 mL) was added and the red color faded to yellow. The solvent was evaporated at room temperature and the resulting aqueous mixture was diluted with 3:1 THF-water (20 mL). The mixture was stirred for 50 h open to the air (and without protection from light), the progress of the reaction being followed by UV measurements (growth of a peak at 510 nm). EtOAc (10 mL) was added and the mixture was washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:0.5:20 acetone:AcOH:CH_2Cl_2, gave tetrahydrohomofredericamycin A (**335**) (2.2 mg, 62%) as a pure (^1H NMR, 400 MHz), red solid: mp 350 °C dec; FTIR (CH_2Cl_2 cast) 2925, 2854, 1745, 1698, 1650, 1605, 1110 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 0.88 (t, J = 7.1 Hz, 3 H), 1.25--1.38 (m, 4 H), 1.58--1.69 (m, 2 H), 1.96--2.09 (m, 4 H), 2.50 (t, J = 8.8 Hz, 2 H), 2.95 (t, J = 6.2 Hz, 2 H), 3.98 (s, 3 H), 6.27 (s, 1 H), 6.36 (s, 1 H), 6.83 (s, 1 H), 8.50 (br s, 1 H), 12.53 (s, 1 H), 12.75 (s, 1 H), 13.19 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ 14.05, 19.13, 22.74, 28.05, 30.48, 31.42, 32.10, 33.37, 57.34, 57.73, 106.29, 108.14, 111.41, 116.54, 116.81, 118.60, 118.71, 133.89, 135.59, 139.14, 142.05, 148.24, 153.03, 153.88, 157.89, 161.82, 177.55, 183.89, 189.44, 200.20, 200.24; mass (HRFAB) m/z calcd for $C_{31}H_{28}NO_9$ (M + H) 558.1764, found 558.1771. Irradiation of the methoxy signal at δ 3.98 in the ^1H NMR spectrum caused a nuclear Overhauser enhancement of 7% in the vinyl hydrogen signal at δ 6.36.

6',7'-Dihydro-1',4,5,6,8,9,9'-heptamethoxy-3'-pentylspiro[2*H*-benz[*f*]indene-2,8'-[8*H*]cyclopent[*g*]-isoquinoline]-1,3-dione (448).



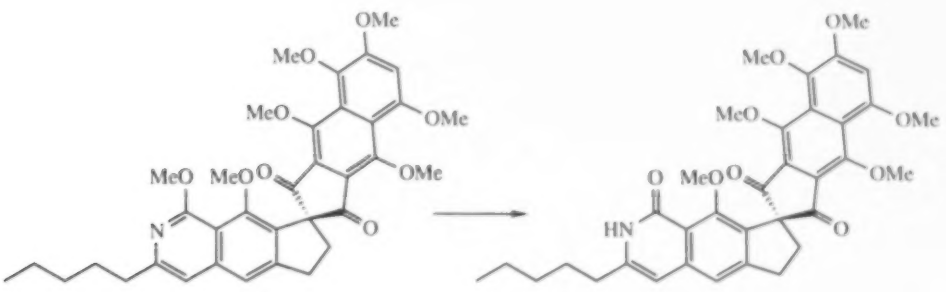


t-BuOK (28 mg, 0.248 mmol) was added to a stirred suspension of (*E*)-2-butenylmethyldiphenylphosphonium iodide[133] (94 mg, 0.246 mmol) in THF (1 mL), and the mixture was stirred at room temperature for 20 min. A portion of the resulting orange-red suspension (0.8 mL) was added to a stirred solution of aldehyde **446** (20 mg, 0.034 mmol) in THF (1.5 mL) at room temperature. After 5 min, the mixture was evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 15 cm), using 3:2 EtOAc-hexane,

gave alkenes **447** as a mixture of three isomers, which was used immediately in the next step.

Pd/C (10%, 5 mg) was added to a stirred solution of alkenes **447** in EtOAc (1 mL) under Ar. Stirring was continued under H_2 (balloon) overnight at room temperature. The suspension was filtered through a pad of silica gel (3 x 2 cm), using EtOAc. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 3:2 EtOAc-hexane, gave **448** (16 mg, 75%) as a pure (^{1}H NMR, 400 MHz), yellow foam: FTIR (CH_2Cl_2 cast) 2960, 2850, 1732, 1702, 1630, 1350, 1340, 1020 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.92 (t, J = 7.0 Hz, 3 H), 1.30--1.41 (m, 4 H), 1.72--1.82 (m, 2 H), 2.51 (t, J = 7.0 Hz, 2 H), 2.71 (t, J = 7.4 Hz, 2 H), 3.34--3.39 (m, 2 H), 3.40 (s, 3 H), 3.88 (s, 3 H), 3.99 (s, 3 H), 4.01 (s, 3 H), 4.02 (s, 3 H), 4.03 (s, 3 H), 4.05 (s, 3 H), 7.95 (s, 1 H), 7.00 (s, 1 H), 7.39 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ 14.20 (q'), 22.97 (t'), 29.10 (t'), 31.89 (t'), 32.75 (t'), 36.43 (t'), 37.70 (t'), 56.91 (q'), 57.49 (q'), 62.15 (q'), 62.81 (q'), 63.11 (q'), 63.33 (q'), 66.67 (s'), 100.09 (d'), 111.55 (s'), 112.57 (d'), 117.50 (s'), 121.35 (d'), 124.84 (s'), 127.93 (s'), 131.47 (s'), 135.21 (s'), 139.71 (s'), 143.54 (s'), 150.47 (s'), 151.31 (s'), 152.68 (s'), 153.46 (s'), 154.27 (s'), 154.30 (s'), 157.20 (s'), 159.40 (s'), 199.55 (s'), 200.62 (s') (two methyl signals overlap); exact mass *m/z* calcd for $C_{36}H_{39}NO_9$ 629.2625, found 629.2919.

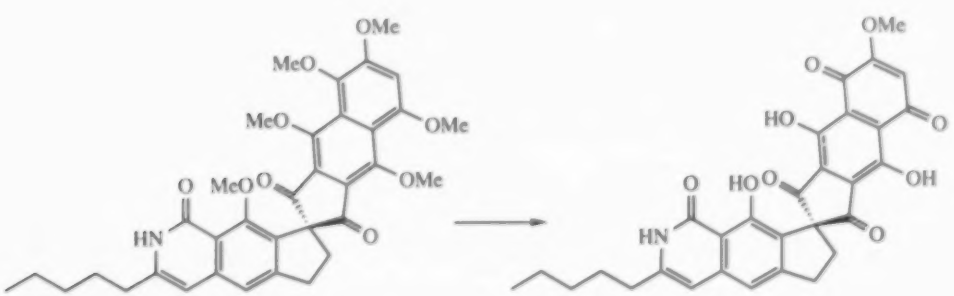
6',7'-Dihydro-4,5,6,8,9,9'-hexamethoxy-3-pentylspiro[2*H*-benz[f]indene-2,8'-[8*H*]cyclopent-[g]isoquinoline]-1,1',3(2'*H*)-trione (449).



TMSCl (25 μL, 0.20 mmol) and NaI (4.8 mg, 0.032 mmol) were added to a stirred solution of **448** (16 mg, 0.025 mmol) in a mixture of CH_2Cl_2 (2 mL) and MeCN (2 mL). Stirring under Ar was continued for 1 h at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using EtOAc, gave **449** (13.1 mg, 84%) as a pure (^{1}H NMR, 400 MHz), yellow foam: FTIR (CH_2Cl_2 cast) 2930, 1732, 1702, 1640, 1617, 1360 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.78--0.82 (m, 3 H), 1.20--1.33 (m, 4 H), 1.58--1.70 (m, 2 H), 2.41--2.53 (m, 4 H), 3.28--3.37 (m, 2 H), 3.47 (s, 3 H), 3.88 (s, 3 H), 3.99 (s, 3 H), 4.01 (s, 3 H), 4.04 (s, 6 H), 6.22 (s, 1 H), 6.95 (s, 1 H), 7.18 (s, 1 H), 10.35 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ 13.98 (q'), 22.68 (t'), 28.04 (t'), 31.41 (t'), 33.01 (t'), 33.21 (t'), 36.06 (t'), 56.89 (q'), 57.47 (q'), 62.12 (q'), 62.40 (q'), 63.08 (q'), 63.29 (q'), 66.64 (s'), 100.08 (d'), 104.13 (d'), 116.61

(s'), 117.66 (d'), 121.33 (s'), 124.83 (s'), 127.89 (s'), 131.41 (s'), 135.37 (s'), 139.71 (s'), 142.60 (s'), 143.52 (s'), 151.29 (s'), 153.31 (s'), 154.22 (s'), 154.27 (s'), 156.34 (s'), 157.18 (s'), 162.45 (s'), 199.57 (s'), 200.66 (s'); exact mass *m/z* calcd for $C_{35}H_{37}NO_9$ 615.2468, found 615.2448.

6',7'-Dihydro-4,9,9'-trihydroxy-6-methoxy-3'-pentylspiro[2*H*-benz[f]indene-2,8'-[8*H*]cyclopent-[*g*]isoquinoline]-1,1',3,5,8(2'*H*)-pentone (450).



BBr_3 (0.53 M in CH_2Cl_2, 0.41 mL, 0.22 mmol) was added in one portion to a stirred and cooled (-78 °C) solution of **449** (13.5 mg, 0.022 mmol) in dry CH_2Cl_2.(2.0 mL) under Ar. The solution became red-purple immediately. Stirring was continued for 1 h and the dry-ice cold bath was changed to an ice bath. After 10 min, water (0.5 mL) was added. The red color faded to yellow. The solvent was evaporated at room temperature and the resulting aqueous mixture was diluted with 3:1 THF-water (80 mL). The mixture was stirred for 48 h

open to the air (and without protection from light), the progress of the reaction being followed by UV measurements (growth of a peak at 510 nm). Most of the THF was evaporated at room temperature under water pump vacuum. Water (5 mL) was added and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:0.5:20 acetone-AcOH-CH_2Cl_2, gave **450**[134] (6.0 mg, 50%) as a pure (^1H NMR, 400 MHz), red solid: mp 350 °C dec.; FTIR (CH_2Cl_2 cast) 2948, 2929, 1747, 1716, 1650, 1610 cm^{-1}; ^1H NMR (400 MHz, CD_2Cl_2) δ 0.92 (t, *J* = 7.2 Hz, 3 H), 1.35--1.39 (m, 4 H), 1.58--1.70 (m, 2 H), 2.43--2.58 (m, 4 H), 3.32 (t, *J* = 6.6 Hz, 2 H), 3.99 (s, 3 H), 6.30 (s, 1 H), 6.36 (s, 1 H), 6.93 (s, 1 H), 8.30 (br s, 1 H), 12.44 (s, 1 H), 12.47 (s, 1 H), 13.20 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.614 MHz) δ 14.02, 22.74, 28.09, 30.14, 31.45, 33.27, 35.30, 57.71, 65.08, 106.90, 111.46, 112.27, 118.69, 124.13, 135.68, 137.35, 141.80, 142.16, 152.81, 155.39, 156.16, 161.90, 168.01, 184.00, 189.55, 199.18, 199.25 (several signals overlap); mass (HRFAB) *m/z* calcd for $C_{30}H_{26}NO_9$ (M + H) 544.1607, found 544.1609.

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